Intelligent decision support systems for optimised diabetes

Andrew D. Jackson-Smale (1993)

INTELLIGENT DECISION SUPPORT SYSTEMS FOR OPTIMISED DIABETES THERAPY

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to Karen and Rhiannon

(No-one with a young child should ever write a thesis)

ABSTRACT

Computers now pervade the field of medicine extensively; one recent innovation is the development of intelligent decision support systems for inexperienced or non-specialist physicians, or in some cases for use by patients. In this thesis a critical review of computer systems in medicine, with special reference to decision support systems, is followed by a detailed description of the development and evaluation of two new, interacting, intelligent decision support systems in the domain of diabetes.

Since the discovery of insulin in 1922, insulin replacement therapy for the treatment of diabetes mellitus has evolved into a complex process; there are many different formulations of insulin and much more information about the factors which affect patient management (e.g. diet, exercise and progression of complications) are recognised. Physicians have to decide on the most appropriate anti-diabetic therapy to prescribe to their patients. Insulin-treated patients also have to monitor their blood glucose and decide how much insulin to inject and when to inject it.

In order to help patients determine the most appropriate dose of insulin to take, a simple-to-use, hand-held decision support system has been developed. Algorithms for insulin adjustment have been elicited and combined with general rules of therapy to offer advice for every dose. The utility of the system has been evaluated by clinical trials and simulation studies.

In order to aid physician management, a clinic-based decision support system has also been developed. The system provides wide-ranging advice on all aspects of diabetes care and advises an appropriate therapy regimen according to individual patient circumstances. Decisions advised by the physician-related system have been evaluated by a panel of expert physicians and the system has undergone informal primary evaluation within the clinic setting. An interesting aspect of both systems is their ability to provide advice even in cases where information is lacking or uncertain.

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CHAPTER 1 - DECISIONS AND DIABETES

INTRODUCTION

This thesis addresses a difficult and critical domain of medical decision making - diabetes care. Diabetes is one of the most common chronic diseases; it is an unusual medical problem in that patients make many of the decisions about how to manage the disease themselves. The role of the diabetes health care team, which includes general practitioners, nurses, diabetes specialists and various other medical specialities is to support patients and to educate both them and their families in this management process in order to alleviate the many potential problems of the disease.

It is known that both physicians and patients experience problems with decisions of anti-diabetic therapy adjustment and it is thus a fertile area for decision support. Expert physicians have traditionally been consulted on a regular basis and help is almost invariably available by telephone. However, a cheaper, less obtrusive and more easily accessible form of decision support would be distinctly advantageous to patients and physicians. The growth of "Artificial Intelligence" (AI) and the increases in computer power and availability over the last decade has provided the platform for the development of practical intelligent decision support systems.

Physicians have to decide on an appropriate initial therapy and make decisions about the long term management of patients and individual problems (complications, metabolic disturbances etc.) as they arise. Patients, however, have to make decisions on a day to day basis in relation to their glycaemic control. The two different rôles suggests a divide in the therapy decision-making equipment. Two systems are needed and two decision support systems are presented in this thesis; the first is a portable, hand-held system appropriate for use by patients and the second is a conventional microcomputer-based system for use by physicians. It should be plain from the title "decision support" that the systems are provided in order to help make decisions, they are augmented by good health care and, if used properly, augment that health care. The use of such systems is a move towards a more hopeful outlook for diabetes in the next decade.

Outline of Thesis Structure

- In chapter one, the nature of decision making is discussed and some background on diabetes is given.

- In chapter two, a discussion of intelligent computer systems is presented, with particular attention to the role of decision support systems.

- Chapter three summarises existing computer systems in diabetes care.

- Chapter four describes the development and evaluation of the hand-held decision support system aimed at patients (POIRO)

- Chapter five covers research, development and evaluation of the physician-related decision support system (PRESTO).

- Chapter six contains the Conclusion.

DIFFICULTIES IN CHOOSING AND ADJUSTING ANTIDIABETIC THERAPY

People with diabetes have to make difficult daily decisions about their therapy. In many cases, every meal and corresponding insulin injection have to be calculated to maintain the blood glucose level of their bodies within reasonable upper and lower limits. The knowledge which enables them to make these decisions comes from their health care team and from their own knowledge gained from experience. There is thus a learning process, which may be quick and easy for some people, but is more often a painful process of trial and error. Learning the techniques of insulin use comes at the same time as patients are trying to come to terms with their diagnosis; therapy adjustment is thus often not given as much consideration as it deserves.

Along with insulin therapy come possible unpleasant side-effects: too much insulin leads to very low blood glucose - a condition known as hypoglycaemia (see later). Patients are therefore often reluctant to alter insulin doses for fear of hypoglycaemic reactions and

consequently blood glucose values remain unacceptably high. Algorithms for adjustment of insulin dosage became available more than ten years ago (Skyler et al 1979), but the number of factors involved, and the effort required to follow the algorithms, make it difficult for all but the most dedicated and well-motivated patient to apply them for each and every insulin dose successfully, (patients typically have to administer three or four insulin injections per day).

A major step forward came with the development of miniature blood glucose sensors. Patients now have the capability to carry out accurate blood glucose monitoring at home. The advent of home blood glucose monitoring was not however a solution to the problems of calculation of the optimal insulin dose and further work was needed to provide patients with the information of how to use their monitoring effectively.

Computers provide an answer to the problem of calculating the correct insulin dose for patients. In order to be acceptable to patients and their physicians the computer should be reliable and able to adapt to the individual requirements of each patient. In addition, for ease of use, portability is an important requirement. Portable insulin dosage computers have been in existence now for over six years (see chapters 3 & 4). Early systems had many drawbacks, they had small memory size, keyboards and display. Consequently, their use was restricted to the dedicated few who were willing to carry out regular, four times per day blood glucose measurements and stick rigidly to a regular diet and activity plan.

POIRO and PRESTO - Two new intelligent decision support systems

This thesis describes the development of a new decision support system - the Patient Oriented Insulin Regimen Optimiser (POIRO) which has been designed to calculate and advise insulin doses to insulin-requiring diabetics based on a) the information they supply and b) the response to previous advice, assessed by home blood glucose monitoring. The device is designed to adjust insulin doses on an individual basis with the minimum of impact on lifestyle. Simple, relative methods of entering information have been incorporated which mean that no complicated dietary analysis or weighing of food is necessary. The insulin doses prescribed by the physician are adjusted from day to day depending on the response to previous doses;

prospective adjustment is also made for cases of non-standard factors, such as ill health or a large or small meal. POIRO is described, along with its reasoning and algorithms, in chapter 4.

Diabetes "mini-clinics" are currently a popular development in general practice. It has been documented, however, that many GPs often experience uncertainty, even with fairly commonplace decisions (Rector et al 1989); in particular less than a quarter of GPs are confident about initialisation and management of insulin therapy for patients. This thesis looks at decision making and especially medical decision making with emphasis on diabetes. A system which offers expert advice to physicians about control and management of both type I and type II diabetes has been designed and implemented as a research prototype. The Physician-Related Expert System for Therapy Optimisation (PRESTO) covers all factors relevant to the different types of diabetes therapy: diet, tablet and insulin replacement. Wide ranging advice concerning factors such as the amount of monitoring, diagnosis and treatment of complications is also incorporated. As there are many different levels of expertise among GPs (both medical and computer) the system has been designed to permit different levels of abstraction for data entry. This enables its use by physicians at all levels for informed, co-operative decision support. The highest abstraction level represents management and control information as fuzzy symbolic quantifiers entered directly by the physician, for instance level of glucose before breakfast (the fasting glucose) may be entered as "low", "normal", "high" or "very high". The system is rule-based, uses structural representation techniques and incorporates a degree of default reasoning in cases of missing data.

It is hoped that with further resources the two systems could be integrated to provide a comprehensive system for the management of diabetes care. At present, PRESTO has a facility for initialisation of POIRO but no further data transfer capabilities have been utilised. POIRO has been assessed in clinical trials and is now relatively stable in format and level of advice. It is hoped that commercial backing will promote more widespread availability of the system at a realistic cost. PRESTO has undergone informal evaluation in the clinical setting and with a panel of physicians. Validation and evaluation of intelligent systems forms a central role in

their eventual acceptance and new techniques are examined and recommendations made for further evaluation and validation of the system at the end of chapter 5.

It is thought that some of the techniques used in the abstraction of data may be applied in other medical domains, particularly in the management by medical protocols of other chronic diseases which require regular assessment and therapy adjustment. Such is the modular design of the system that it would be possible to employ the basic facilities for data management and apply the system to other chronic conditions, for example asthma, which require long term monitoring and decision making.

DECISION MAKING

Decisions have to be made in all walks of life in various situations. Usually the consequences of decisions are not crucial but sometimes critical decisions have to be made. People develop general decision making skills from childhood, their ability to pick up knowledge about the environment and to learn from experience is phenomenal. At the other end of the scale, there now exist expert decision makers; they have studied a small field of knowledge and practised decision making in that field for many years.

The complexity of some situations where decisions have to be made, for instance in urban planning, financial budgeting and medicine has given rise to a number of tools, both theoretical and practical, designed to aid the decision making process. Modern information gathering equipment has developed at a much faster rate than the development of theories and techniques for sensibly collating and using the information supplied. Some of the developments and a historical overview of them are given in chapter 2. This section deals more with the definition of decisions and how theoretical considerations may be used to make these decisions in the most profitable way.

The processes by which humans learn to make decisions are not well understood and it is only recently that general theories of problem solving/decision making have been developed. Recent

research has produced theories of decision making and some of these are outlined below, first though we have to define what decisions are and how they are taken in practical situations.

What is a Decision?

The Concise Oxford Dictionary defines a decision as "the settlement of (question etc.), conclusion, formal judgement, making up one's mind". The verb "to decide" comes from the same linguistic root as the nouns scythe and scissors; it has the meaning "to cut". Essentially, a number of *options* are cut down to a final *choice*. The processes involved in reaching decisions are complex, but some generalisations may be made: an assessment of the benefit of the potential outcomes is involved in some form but also decisions take into account the level of cost or risk involved.

One type of analysis is known as the maximisation of expected utility (Lindley 1984). Utility may be defined as the benefit of a possible outcome divided by its cost. The method of maximising expected utility is actually described by Lindley as the *only* correct approach to decision making. It has a well-defined procedure: first, the uncertainties present in the situation must be quantified in terms of values called probabilities. Second, the various consequences of the courses of action must be similarly described in terms of utilities. Third, that decision must be taken which is expected, on the basis of the calculated probabilities, to give the maximum utility.

Experiments have been carried out for over twenty years using the numerical approach of maximising expected utility. Some of the experiments were in domains where the extraction of the numerical values was tractable and these produced accurate, working systems (De Dombal 1972). However, the adoption of formal decision methods was limited, in the medical domain especially, due to the lack of clear definitions and quantitative data on the potential courses of action (step one of the theory). The demand for quantitative data was particularly disliked by the users, in particular the assessment of the utility of outcomes in medicine is rarely objective and subjective estimates differ between different situations for different users.

Other important concepts involved in framing decisions are the decision maker's level of ignorance and so-called risk attitude. The level of ignorance may be defined within a taxonomy of levels and affects the depths of analysis and user assessment which may be called upon in decision making in a particular domain. The risk attitude is defined as the decision maker's willingness to be exposed to risk. It is intrinsically linked to medical decisions when possible outcomes involve a risk of an unfavourable effect.

In virtually all decision situations some level of ignorance applies; the level of ignorance is central to the level of decision support required and the potential decision contexts which may be used. Ignorance may be classified into a taxonomy of levels (Holtzmann 1989). The highest level (i.e. the level at which ignorance is least) is the combinatorial level; problems at this level have an appropriate model and methods of solution but the problem is so large that the methods cannot be applied using currently available technology. Second, the Watsonian level of ignorance, this is the level of ignorance of Dr. Watson in relation to Sherlock Holmes. The model is available but the solution method is incomplete, exemplified in the phrase "..elementary my dear Watson" (never actually used by Conan Doyle, probably originated in Hollywood). The third level is named Gordian after the knot tied by Gordius for the future ruler of Asia to untie. Alexander, like everyone else, could not untie the knot so he cut the rope with his sword. At the Gordian level the model is incomplete and the problem has to be reformed in order to be solved. The fourth level is termed the Ptolemaic level, the model is complete but very awkward, Ptolemy's theory of planetary motion required many exception rules in order to work, Copernicus provided a new model which led to Kepler and Newton's formation of the accepted theory. At the next level, a model works but no one knows quite why it works, for this reason it is called the magic level. When no model is available, the dark level, there is no clear method to make decisions although the problem is known. The lowest level is the fundamental level in which the "problem" is not even realised to exist.

The statistical assessment of risk (risk analysis) is a highly specialised theory. In practical situations, experts have to "weigh up" risks associated with certain choices, against the benefits

of each option. The example from diabetes given earlier in this chapter is a good example of the complexities involved in real-life medical decision making. Patients are worried by the risk of hypoglycaemic reactions due to excess insulin and consequently do not attempt to reduce the blood glucose to normal levels; the risks of long term problems may not be rated as important by patients until symptoms of complications appear. The ultimate risk is to life itself, but along the way there are considerations of quality of life which must be taken into consideration if medical help is to be optimally employed. Individuals will form their own opinions about risk but should be well informed of the potential risks in order to make the value judgements necessary for the assessment.

Another consideration to be taken into account in practical decision making is that decisions should, in general, feel intuitively correct and there should be some level of justification, or explanation at a level which may be comprehended by the user. Users frame individual decision contexts within an overall decision model which has been previously defined. The user will be more likely to make use of a decision support system (DSS) if a sense of "ownership" is felt for the decision context. This is especially true of the medical domain. Users will also be reluctant to accept decisions which do not agree with intuition without clear, understandable justification and explanation of why the decision was made.

An example from diabetes is that, in general a high blood glucose will lead to advice to raise insulin. However, a raised fasting blood glucose may be due to excessive overnight insulin; this has been documented in the literature and is termed the Somogyi effect (Somogyi 1959); (although note that some evidence points against the existence of the effect (Gale 1980)). In order to convince physicians that their intuition may be wrong, a thorough explanation of the criterion used to give the advice may be required. Problems with patients may involve their intuitions of which insulin dose affects which blood glucose result: this is an example of the Ptolemaic level of ignorance, although in some ways it is worse as the patient's mental model is incorrect.

The considerations of risk attitude, ignorance level and the intuitions of the decision maker define the decision situation. The decision domain is defined by the problem to be solved, the possible outcomes and the variable factors which enter into the decision. The union of the decision domain and the decision situation is termed the decision context, the context will include a set of constraints; these may be hard constraints which are inviolable, or soft constraints which reflect the cost of utilising certain resources. Hard constraints may be natural, such as the constraint on the number of hours in a day or else they may be defined on moral and ethical grounds.

Once a decision has been framed and all the available relevant information has been collated, a decision may be taken. A decision is an instance of an action; it is defined as the action of allocation of resources (Lindley ibid.). The action in turn then leads to an outcome which may be one of the considered options or may be an unexpected outcome. If the outcome had not been considered then the decision model was incorrect or incomplete. If the outcome may be related to the original set of options, the model may be assessed for the quality of its decision: however, this need not be a simple comparison of expected and actual outcomes. It is possible for a seemingly correct decision, based on all the available data, to result in an undesirable outcome; the opposite is also true: a bad decision may lead to a favourable outcome; this would involve what we normally term "luck". Remember that according to the utility model, a decision is taken which is likely to be beneficial and minimise risk; in a single instance of a process however, an unlikely outcome may occur. The evaluation of a decision is thus a difficult problem, if many equivalent decisions have to be made, based on the same initial criteria, then statistical analysis may be used to show that the decision is optimal more times than not. In other cases, the decision may be compared to a "gold standard", defined by consensus among experts in the domain as being the outcome with the highest utility.

CLINICAL DECISION MAKING

In the past few decades there have been many improvements in clinical science due to increased understanding of the means of relief, comfort and healing. At the beginning of the study of medicine, knowledge was passed down by teachers; this knowledge was augmented in stages by investigators who carried out experiments which interested them and eventually methods were established for the dissemination of discoveries and results. In this way medicine became established as an empirical science, based on the disciplines of anatomy, physiology and biochemistry. The natural changes in time of the body due to degenerative processes were distinguished from processes which were due to unnatural changes brought about by disease. The study of diseases, with a view to finding control and future prevention became known as epidemiology, this now forms the backbone of much practical medical practice. Epidemiology relies on associative links which are statistically proven to exist, for example between diseases and their signs and symptoms.

New discoveries in medicine may lead to new unanswered questions and new problems: the discovery of insulin lifted the threat of immediate death from diabetics but introduced a whole new set of medical problems due to the long term morbidity of the disease. The learning process in medicine is thus continuous as medical knowledge is relatively incomplete and often tentative. The approach to medicine is often one of model building and definition. The more variables that are included in a model, the more complex are the decisions that have to be handled. The rapid increase in complexity of models as the number of variables increases - the combinatorial explosion - leads to other forms of decision making rather than solely analytical decision making. Problem solving is often done by abductive logic, i.e. the inference of a minor, specific premise from a major general premise and a specific conclusion. In contrast, inductive and deductive logic rely on a more empirical approach. The detail behind complete pathophysiological models is often forgotten in favour of the knowledge or ability to apply the knowledge to the treatment of the "whole body". As Plato said " The wise physician is the best solution".

The sub-divisions of clinical medicine are: medicine, surgery, obstetrics and gynaecology and paediatrics (Martin 1981). In their training, medical students spend a set amount of time in each of these specialties. The most comprehensive of these four major sub-divisions is undoubtedly medicine. The study of medicine is organised around the analysis of patients' signs and symptoms in order to develop initial diagnosis hypotheses. The principle tasks involved may be broken down as follows (Williams 1982): 1) acquire relevant data from the patient appropriate to the circumstances of care and resources available; 2) use this data, in the light of the complete medical knowledge base, to establish diagnosis or a list of problems; 3) establish a plan for management of the problems. 4) monitor progress through iterative data acquisition; this may lead to further investigations which in turn lead to alterations of the monitoring and management plans. Lawrence Weed (Weed 1971) analysed medical tasks into a problem oriented system model, he gave the final stage of the process the acronym SOAP for Subjective evaluation - Objective evaluation - Assessment and Plan. This stage may be thought of as iterations of the 3 prior tasks in the plan.

The involvement of the patient is passive during stages one and two. These stages are largely physician-led once the original problem has been presented by the patient. The third stage involves the patient in the decision and management process to a degree which depends on the specific problem in question. The degree of involvement in diabetes is very high as patients need to monitor their own progress for long periods of time between visits to their clinician.

Clinical Decision Making Paradigms

Now that some of the problems and procedures of medical decision making have been recognised, practical and theoretical methods of actually providing automated decision support may be defined and examined. Automation of decision making falls into three broad categories: the first is termed the categorical approach; the second is the statistical or probabilistic approach and the third is the symbolic reasoning or Artificial Intelligence approach.

Within the categorical approach, clear-cut guidelines are presented, based on well defined and understood criteria. The representation of categorical systems is often made by clinical algorithms. An algorithm is defined as a step-by-step procedure for solving a problem that contains conditional logic. The clinical algorithm can also be viewed as a form of practice guideline. Formal attributes of clinical guidelines have been defined by the American Institute of Medicine; these include reliability, validity and clarity (Margolis et al 1992). One of the main advantages of algorithms is the possibility of their representation as a flowchart - a diagram which explicitly defines all the decision points, the criteria necessary for making the decisions and the outcomes of those steps.

The second approach is sometimes termed the statistical theory of decision making. It has strong theoretical and practical grounding and has been successfully employed in business and finance over the last twenty years. "Statistics" has as one of its definitions: "The science of decision making". The fields of statistics associated with making decisions include point estimation, inference, hypothesis testing, interval estimation and selection procedures (Dudewicz & Mishra 1988). The detail of the formal decision theory will not be given here; instead, an outline of the theory, listing the main components and the general formulation is given.

Two main components of decision theory problems are: distribution of data (or observations) which may be quantified by parameters or may be non-parametric, and the calculation of expected losses or gains due to a decision. In the general formulation of decision theory a random variable X is observed from which a distribution function $F(x|\Theta)$ may be found (the parameter Θ is unknown). A set of decisions D is defined from which a single decision d is chosen which has a loss function $l(\Theta,d)$. Selecting the appropriate decision d is carried out using decision rules of the form $s(x) = d$ after observing x. The risk function $r\Theta(s)$ is defined as the average loss and is the criterion by which rules are compared; (equation E1.1), (E() denotes expected value).

$$r\Theta(s) = E(l(\Theta,s(X))). \qquad \text{(E1.1)}$$

By making these definitions, decision analysis hopes to study general properties of rules and find the appropriate rule to apply in specific cases. There have been many practical applications of decision theory in the physical sciences, but little inroad has been made into medical decision making. Instead, medicine has propagated the use of hypothetico deductive styles of decision making and reasoning. In particular, a statistical approach which has proved popular in medicine in the past has been the application of Bayes theorem.

The well-known theorem of Bayes is given as equation E1.2. It may be applied in various decision making contexts. However, by far the most common use of the theorem is in the diagnosis of a disease where certain probabilities of symptoms ($p(e_j)$) appearing concurrently with the disease (H) are linked to the probability of the symptom appearing in the general population, or the probability of the disease being present in the general population.

$$p(H_i|e_j) = p(e_j|H_i) \cdot p(H_i) / \Sigma p(e_j|H_i) \cdot p(H_i) \qquad \text{(E1.2)}$$

In general, a rational decision rule is to select the disease hypothesis for which the posterior probability $p(H_i|e_j)$ is highest after all items of evidence e_1, e_2, e_3 etc. (signs, symptoms, test results and so on) have been acquired. The Bayesian approach to diagnosis was first applied by Ledley and Lusted (1959); the major restriction to application of the method was the lack of reliable statistics on the prevalence of disease symptoms within the general population. Screening of the general population has increased for some conditions, although reliable data is still difficult to find even in those cases. The popularity of Bayes theorem for decision making systems has declined of late, mainly due to this lack of accurate meaningful probabilities of events and the tedium of transcribing the data into a format suitable for a decision support system (DSS), but also due to the increased development of symbolic decision making via expert systems and AI and the realisation of the power of the theories .

Incidentally, to return to the science of risk analysis and to avoid confusion, Bayes rules, as opposed to the theorem above, are complex statistical rules for evaluation of risk probabilities from the distribution function of an observable quantity. For more information on the use of

these rules and some examples of statistical analysis for decision making refer to chapter 12 of Dudewicz and Mishra (1988).

Cognitive research has shown (Elstein et al. 1979) that statistical methods employing probabilities, the use of Bayes theorem included, are not implicitly used by human decision makers when they reason. However, the use of probabilities is obviously much more suitable for use in computer decision support systems and the methods can best be used to augment the simulation of human problem solving techniques. This is the approach adopted by the POIRO system, where heuristic reasoning-type processes are combined with the type of statistical analysis techniques which make intuitive sense but are not in any way supposed to model a human decision maker's mental process.

The third approach to decision making is more symbolic than numerical and is termed the Artificial Intelligence (AI) approach. The AI approach is less mathematical in formulation but relies on manipulation of symbols and knowledge. More recently, symbolic decision making and argumentation has been proposed as a method which subsumes both decision making paradigms (Krause and Fox 1991).

Most recent decision support systems in medicine have centred on a knowledge based, or artificial intelligence (AI) approach; the approach may be termed symbolic rather than numerical because of the use of manipulation of textual phrases or symbols in order to reason and make decisions. Advantages of the AI approach are the relationship of the knowledge contained in the system to real decision makers, the possibility of a dialogue situation with directed questioning rather than standard lists of questions as involved in statistical analysis and the possibility of explanation and justification of decisions in natural language, although the theory of explanation still requires much improvement.

A further benefit of the AI approach is that the agents which provide the decision support can be made, to some extent, autonomous. That is they do not require to be explicitly put into motion but may exist alongside a clinician during normal data entry and be there to be called

upon when required, or alternatively to spontaneously advise of the detection of problems and suggest possible solutions.

One by-product of the growth of telecommunications facilities is the huge amount of information which may be made available. In the case of medicine, there are a huge amount of laboratory procedures and support services which may be called upon by the practising clinician. Alternatively, data may consist merely of straightforward clinical assessments, or symptoms described by patients. One of the foremost functions of decision analysis is to separate what is relevant to decision making and what is interesting to know, but not necessarily relevant to making a decision. The PRESTO system is an example of a knowledge-based system designed for a limited domain. Its objectives are clearly specified and its domain is concerned with decision support for problems related solely to diabetes and, to a lesser extent, its possible complications.

Knowledge-based systems generally contain a mixture of known facts (knowledge which is certain) and domain heuristics (knowledge which is plausible but not certain). The terminology associated with these systems has grown into a complete subset of computer terminology and methodologies and design software have been produced in order to make the development of the systems more sound and better grounded in theory. A frequent criticism of knowledge-based approaches is the lack of a standard guideline for their production and use; the development can sometimes be *ad hoc* but even with common development methodologies developed for so called knowledge-base "shells", the format of the knowledge may still be inconsistent and a real problem is the degradation of such systems at the limits of the knowledge domain.

Chapter two enlarges on the nature and definitions of artificially intelligent systems and includes a breakdown of the processes involved in the development of an intelligent system. In relation to the general criteria of decision making described earlier, knowledge based decision support systems would seem to find most use at the Watsonian level of ignorance, especially in medicine, where the practitioner is a highly skilled knowledge elicitor but may have problems combining the information to come to optimal decisions. Systems may also be of use at the

Gordian level, where the introduction of unconsidered methods may be an aid to inexperienced physicians. The considerable potential for tutorial expert systems has been realised with time (see the discussion of NEOMYCIN in chapter 2). It may also be possible, with increases in computing power, to provide help at the combinatorial level; more complicated problems may become solvable by faster processors, parallel processors and improved solution algorithms, although this will still have ultimate theoretical restrictions in mathematical terms.

The power of decision making systems is their ability to combine different types of knowledge and belief from various sources into a coherent model and decision: the combination of biochemical investigations, results of clinical tests and information gleaned by direct consultation, psychological and physical, as well as clinical observations may be combined using models and probabilistic weighting in order to give a result.

Computerised decision support systems are a subset of a much broader set of "intelligent" computer systems. Intelligence attributed to computer systems is a topic of much philosophical discussion because of the subjective assessment of whether computers can be considered as intelligent - an argument which is illustrated in Yazdani (1986). For a general definition, a system can be considered intelligent if it provides answers to problems which are on a par with those provided by experts. This definition may cause consternation among readers but is a reasonable working definition for the purposes of defining a goal of AI.

A specific area of knowledge based systems which deserves a mention is that of a critiquing system. Experts can make errors in judgement. A computerised "critic" can assist in the decision making process. A critic is a narrowly focused program that uses a knowledge base to help it recognise what human errors have occurred and what types of criticism might be useful to the human user. Criticism-based problem solving is seen as a novel way to bridge the gap between the knowledge rich approaches of AI and the domain-independent, theory-rich approaches of decision analysis (Silverman 1991). In the past, knowledge-based systems have been designed to deal with trouble-free environments. Future knowledge-based systems will

need to cope with, and preferably take advantage of, the human's intuitive contributions. The critiquing approach is one method of doing just that.

Although critiquing has not been employed directly in either of the systems developed during the work for this thesis, the educational value of the systems is exemplified by the ability of the user, patient or physician, to over-ride any of the system's recommendations. This may then lead to a differential analysis of whether the decision eventually taken by the user was better or worse than the decision which was suggested by the system. Such an analysis would be possible in an extended trial whereby the quantitative measurement of the outcome of the decision (the measured blood glucose levels) gives a clear and comparable assessment of the quality of the decision. This analysis has not been possible so far due to the small amounts of data collected; however, the potential for it should not be overlooked.

The history and development of medical decision support systems will be covered in chapter two, where a general guide to the stages in production of a system is given for the benefit of intelligent system designers. Later, the perspective of medical decision making is examined, with reference to the development of clinical science. However, in order to provide a context for the discussion, some background knowledge about diabetes is appropriate; the next section provides some background for computer scientists who know nothing about diabetes and also provides the clinical reader with a statement of the situation as perceived by the author.

DIABETES MELLITUS

Medical and Cultural History

Diabetes is one of the oldest chronic diseases. First documented by the Ebers papyrus (1500 BC), the name "diabetes" was coined by Demetrios of Apamaia in the second century BC from diabainein, the Greek word for through-passer. The term was used in connection with a siphon used for tapping wine and refers to the commonest symptom of the disease - a passing of large amounts of urine (polyuria).

The first systematic study of diabetes was done by Aretaios (81-138 AD), who characterised diabetes as consisting of intolerable thirst, burning in the intestines, passage of large amounts of urine and having two stages, chronic and acutely fatal. Galen (129-199 AD) included diabetes in his compendium of medical knowledge but admitted he had only seen two cases; this highlights the comparative rarity of the disease compared to today. Diabetes is described in Chinese medical records dating from the second century AD which seem to be the first to mention sweetness of the urine. Arab physicians of the middle ages were very familiar with the disease, Avicenna (980-1037) named the disease Aldulab (waterwheel), because of the almost immediate excretion of the large amounts of water drunk by sufferers. Avicenna also seems to have distinguished harmless diuresis and severe diuresis, diabetes insipidus and diabetes mellitus. In India, Sanskrit medical texts describe characteristics of the urine, but, as with the Chinese and Arab observations, the knowledge did not reach Europe until much later.

The Renaissance in Europe saw Paracelsus (1493-1541) describe the syndrome of excessive urination, thirst and wasting under the name diabetes. In 1674 Thomas Willis tasted urine and found it to be sweet; he added the adjective mellitus, meaning honey, to describe this observation. Matthew Dobson isolated "brown sugar" from the urine of diabetics in 1776 and in 1780 Francis Home developed a fermentation test used as a standard procedure to diagnose diabetes mellitus.

Treatment with diets free from sugar were developed in the nineteenth century, these diets were mostly severely restrictive and, while they did have some measure of success (prolonging 'life' for up to three years). The restrictions imposed (for example no food containing carbohydrate) were agonising for the patients who undertook them; their quality of life deteriorated as they lacked energy and became painfully thin before inevitable death.

Meanwhile, investigations of the pancreas were being carried out. A Swiss physician Johann Conrad Brunner performed an amazing experiment in 1685. He opened up a dog and tied the connections between the pancreas and the rest of the body. Subsequently the dog developed diabetic symptoms: polyuria, polydipsia (excessive thirst) and polyphagia (excessive eating).

Brunner's experiment was not widely disseminated so the link between the pancreas and diabetes remained to be discovered by von Mehring and Minkowski who carried out their epoch-making experiments in 1889 at the Hoppe-Seyler institute in Strasbourg. They surgically removed the pancreas of several dogs, in order, it seems, to see if the organ was necessary for life. They observed the symptoms of diabetes and Minkowski tested the urine, found it to contain 12% sugar, and announced the findings to the world.

Twenty years before Minkowski put forward the link between the pancreas and diabetes, Paul Langerhans had reported the discovery of clusters of cells within the pancreas which were unlike the ordinary tissue of the gland. He gave the cells the romantic name of the islets of Langerhans. Experiments in which the pancreas was removed but the islets left intact showed that it was these cells which had a fundamental role in glucose metabolism. The cells make up approximately 2% of the weight of a human pancreas and have been classified into different cell types.

The most important discovery in the whole history of diabetes to date came in 1922 when Banting, Best, Macleod and Collip isolated insulin and successfully used it to control glycaemia in humans (Banting and Best 1922); Banting and Best were awarded the Nobel prize for the discovery which heralded a new dawn in diabetes research. In his fascinating account of the breakthrough Bliss (1983) quotes the great American diabetologist Elliot Joslin who compared the 'near resurrections' brought about by insulin to the effect of the prophecies of Ezekiel in the valley of dry bones: '... and the breath came into them, and they lived, and stood upon their feet, an exceeding great army.'

Diagnosis

Of the many problems associated with diabetes, diagnosis is perhaps the easiest; the symptoms are easily recognisable and stringent criteria for interpretation of oral glucose tolerance tests (OGTT) have been laid down by the World Health Organisation (WHO) for use in borderline cases (table 1.1); the results of this test divide patients into those with diabetes mellitus (DM) and those with impaired glucose tolerance (IGT), which may or may not develop into diabetes.

Table 1.1 Interpretation of Oral Glucose Tolerance Test, diagnosis of Diabetes Mellitus or Impaired Glucose Tolerance.
For a glucose load of 75g in 250 to 350 ml of water for adults and 1.75g per kg body weight up to 75g for children:

	Glucose concentration (mmol/l)			
	(Whole blood)		(Plasma)	
	venous	capillary	venous	capillary
Diabetes Mellitus				
Fasting value	≥ 6.7	≥ 6.7	≥ 7.8	≥ 7.8
2h after glucose	≥ 10	≥ 11.1	≥ 11.1	≥ 12.2
Impaired glucose tolerance				
Fasting value	< 6.7	< 6.7	< 7.8	< 7.8
2h after glucose	6.7-10	7.8-11.1	7.8-11.1	8.9-12.2

In addition to impaired glucose tolerance, there are two major types of diabetes defined by the WHO: Type I, or insulin-dependent diabetes mellitus (IDDM) and Type II, or non insulin-dependent diabetes mellitus (NIDDM).

Type II diabetes is the most common; it can often be controlled successfully by following a strict diet, or by tablets, but occasionally needs insulin replacement therapy. Type II diabetes may be present for a long time before the glucose level rises to a symptomatic level; many type II diabetics are thus detected by screening or as a secondary finding when another medical condition is detected. Sometimes diabetes may be present alongside other diseases or syndromes; in other cases it is detected by the diagnosis of another problem, such as hyperlipidaemia, which is known to be a secondary development of diabetes. The susceptibility to type II diabetes increases with age, which is why it is often called maturity-onset diabetes. However, type II diabetes may affect young people, in which case the sub-type *MODY* (maturity onset diabetes of the young) may be suspected. Recent research has suggested a strongly inherited link in diabetics of this type (O' Rahilly et al. 1987).

Type II diabetes often manifests itself in women during pregnancy when it is known as *gestational* diabetes. Diabetes may relent once gestation is complete, only to return later in life, either at a subsequent pregnancy or due to weight gain or old age; it is particularly important to strive for normoglycaemia during pregnancy, in order to reduce foetal morbidity and mortality

(Essex 1976). Other specific sub-types of type II diabetes have been documented but most are extremely rare and the diagnosis does not, in most cases affect the therapy to be used.

The onset of type I diabetes is much more acute, it always requires exogenous insulin replacement therapy, and it is invariably much more difficult to control. Type I diabetes is often described by the term *juvenile-onset*; as it has its highest incidence below the age of 20; strictly however, the term is incorrect, as type I diabetes may occur at any age. Detection of type I diabetes is usually by observation of symptoms (table 1.2) although new methods of detection are becoming available for those known to be at risk (see below).

Table 1.2 Most common symptoms of Diabetes Mellitus

Excessive thirst	(polydipsia)
Frequent urination	(polyuria)
Frequent night-time urination	(nocturia)
Weight loss (type I only)	
Visual disturbances	
Skin irritation	(pruritis)

Type I diabetes is thought to have an autoimmune pathogenesis; evidence for this includes the finding, at diagnosis, of infiltration of the islets of Langerhans with inflammatory cells, circulating islet cell-specific antibodies and alterations in circulating T cell subsets (Fletcher and Barnett 1989). Studies in identical twins (Barnett et al 1981) have suggested the existence of an environmental agent that triggers diabetes in genetically predisposed individuals.

Genetic research has centred on the HLA (or major histocompatibility complex) system although there is growing evidence that an HLA linked predisposition does not fully explain the genetic basis of type I diabetes. Despite the enormous effort none of the central questions regarding causation has received a definitive answer. Factors to be uncovered include the relative contributions of environmental and genetic factors and the number and identity of genes involved.

Wilkin (1990) describes different islet cell antibody types and compares their value in predicting diabetes using statistics of how the disease progresses in individuals screened early for the disease; i.e. first degree relatives of diagnosed diabetics. He concluded that the

detection of islet cell antibodies (ICA) may mean that type I diabetes can be predicted before clinical onset.

The majority of type I diabetics experience a temporary remission during the early stages of diabetes. The need for exogenous insulin falls and may decrease to zero as the patient's capability to produce endogenous insulin recovers with the introduction of insulin replacement therapy. This is always a temporary remission and has therefore been given the name of the "honeymoon" period. It lasts for up to about a year in some individuals but is usually shorter in duration. There have been studies in which certain preventative drugs have been tested to see if the honeymoon period may be extended. So far, the drugs used (for example cyclosporin) have been only partially effective (Moncada et al 1991).

The family study, undertaken jointly in Oxford and Birmingham (Barnett and Todd 1990) concentrated on families with at least 2 diabetic siblings and examined DNA for the specific genetic susceptibility which causes diabetes. If such studies are successful there would still be an urgent need for a preventative drug. Cyclosporin, probably the most effective drug in prolonging remission yet tested, is toxic and so cannot be taken long term.

Pathophysiology

There are many examples in physiology of feedback control of body mechanisms. Many of these systems use hormones as the messengers of control. One typical example is the control of the amount of glucose in the blood. Glucose is the body's natural energy source; it is provided by food and utilised by all body tissues, primarily the muscles and the brain. The liver plays a large part in the regulation and storage of blood glucose (Horner Andrews 1979), but the most important hormone - insulin - is secreted in the pancreas. Although the primary function of insulin is the maintenance of homeostatic balance of serum glucose concentration, it does have other functions (e.g. lipogenesis in adipose tissue). All hormones are chemical messengers; they work by feedback regulation of secretion. In glucose homeostasis an elevation of glucose is sensed by the pancreatic islet B cells, which secrete additional insulin, this results in a

decrease in glucose concentration by promoting its transfer into cells. As glucose falls, the rate of insulin release decreases until normal levels are regained once again.

The pancreatic islets contain four types of cell which produce four hormones (Martin et al 1981). About 25% of the cells are "A" type, these produce glucagon. Insulin is produced in the "B" cells which make up 60% of the number; insulin forms a "bihormonal" unit with glucagon. Insulin facilitates entry of sugars, notably glucose, into cells, where phosphorylation occurs converting glucose into other products, including glycogen. Glycogen is stored in the liver, adipose tissue and muscles and may be utilised, under the action of glucagon, in times of glucose shortage. Somatostatin is produced in the 10% of cells which are known as "D" cells. Somatostatin has the interesting property of inhibiting insulin production, although its main function is hypothalamic. The fourth hormone, pancreatic polypeptide is present in the "F" cells; it has glucagon-like glycogenolytic activity but its functions are mainly gastrointestinal.

Insulin synthesis occurs in stages; proinsulin is synthesised in the islets as a single polypeptide chain of 86 amino acid residues. Cleavage then occurs making a single chain C-peptide and the dual chain insulin hormone; thus, the measurement of C-peptide in diabetics gives a measure of insulin synthesis by residual B cell function as C-peptide is produced in equimolar proportions to insulin. All the hormonal functions of insulin are anabolic, as opposed to most hormones whose actions are catabolic. Its effects increase the rate of synthesis and storage of protein and energy reserves, glycogen and lipids.

The normal physiological profile of glucose and insulin dynamics is a remarkable control system. During fasting, a small trickle of insulin is necessary to achieve a basal normoglycaemic state. At meal times glucose is quickly absorbed from carbohydrates and insulin levels increase sharply to counteract a rise in serum blood glucose. The mechanisms are so efficient that glucose rarely rises above 6 mmol/l or falls below 4 mmol/l. During heavy exercise, glucose is utilised in the muscles and blood glucose falls; in this case glucose needs to be provided, and the liver converts glycogen back into glucose by glycolgenolysis. The drop in insulin, accompanied by an increase in glucagon, conserves glucose for the brain and stops the

muscles running the glucose down. The drop in insulin and the rise in adrenaline also causes fat tissue to release fatty acids for use by the heart and skeletal muscles in cases of heavy prolonged exercise.

Diabetes may best be described as a metabolic disorder affecting the beta cells within the islets of Langerhans in the pancreas. The result is an absolute or relative deficiency of the hormone insulin. When insulin is absolutely deficient (as in type I diabetes), glucose builds up in the blood and is then wastefully excreted in the urine. The kidneys work continuously to rid the body of the excess glucose and this leads to excessive urination and insatiable thirst. In time, the body, unable to obtain its energy in the usual way, begins to consume itself by breaking down fat cells. This process is very inefficient and produces organic acids known as ketone bodies; these ketone bodies provide an important alternative energy source for the brain when present in small amounts but, if diabetes is untreated, ketone bodies accumulate in the blood stream and pour over into the urine. Eventually the level of ketones becomes critical and ketoacidosis occurs, followed by coma and death.

For type II diabetes, there are two processes which contribute to raised blood glucose: insulin deficiency and insulin resistance. Insulin works on cells by binding to receptor sites (Van Obberghan 1981). In obese people these receptor sites become more resistant to insulin uptake and this is known as insulin resistance. However, the mechanisms which cause type II diabetes are still not fully understood. Mathematical models of the relative contribution of insulin resistance and insulin deficiency to raised glucose levels have shown that at normal weight, glucose is not elevated until more than 80% of B cells are destroyed (Turner et al 1982). Therefore, by losing their excess weight, type II diabetics may return to normal levels of glucose and insulin although they can never actually be cured of diabetes.

DIABETES THERAPY

There is still, as yet, no cure for diabetes but there do now exist at least three main treatment options: diet therapy, oral agents and insulin replacement therapy. Initially, the control of

blood glucose is important in order to alleviate symptoms of the disease and to prevent diabetic coma due to ketoacidosis. In the long term, many diabetic patients develop complications. Among the most common are serious complications such as heart disease, renal failure and blindness. There is an increasing body of evidence that close control of blood glucose may prevent the progression of the diabetic tissue damage thought to be responsible for these complications (Skyler et al 1987).

The United Kingdom Prospective Diabetes Study (UKPDS) is a large-scale randomised follow up study of 5000 type II (non insulin-dependent) diabetes patients which aims to provide unbiased statistical evaluation of the optimal therapy to prevent complications and to control the blood glucose. The Diabetes Control and Complications Trial (DCCT) in the USA is a similar study of type I patients and should provide clues to the optimal management strategy in insulin therapy. However, until such studies provide conclusive evidence, it is generally agreed that optimal intensive insulin replacement therapy should be the aim of diabetes therapy for type I diabetics alongside effective education of patients and their families and continual medical and psychological support.

The recommended rehabilitation process in patients with diabetes (Howorka et al 1990) is first to provide information about literature, different strategies of treatment and introduce blood glucose self-monitoring. Second, a practical and in depth discussion about diabetes and how it affects the people involved. For insulin treated patients there may then follow a discussion of functional insulin use and simple insulin adjustment algorithms may be introduced. Patients learn from this how to control glycaemia through immediate correction of blood glucose measurements which are off target levels (primary adjustment of insulin dosing), and how to optimise algorithms for insulin use (secondary insulin adjustment). This is followed by an ongoing process of updating the patient's knowledge and practical skills.

Monitoring of Blood Glucose and Its Interpretation

Up until 1976, urine glucose measurements were the only available tests carried out by diabetics to routinely monitor their glycaemic control. However, it was well known that the

renal threshold of most people corresponds to a blood glucose level of approximately 10 millimoles per litre (mmol/l), a value which is unacceptably high compared to the normal level of about 5 mmol/l. Since that time, home blood glucose monitoring (HBGM) (Sonksen et al 1978) has become much more available and simple. This is due to advances in the determination of blood glucose levels quickly and accurately, with a small sample of blood from a finger prick. This has made daily monitoring possible for all diabetics and rules for therapy adjustment, based on accurate blood glucose determinations, have since been published (Skyler et al 1981).

An exception to this rule may be some patients who are on minimal treatment. A single fasting blood glucose determination carried out at regular intervals at diabetic outpatient clinics (or by a primary care physician or nurse) may be sufficient to ascertain overall quality of control, and occasional checks via urine monitoring may be all that is required of the patient at home (Holman and Turner 1988).

In addition to home blood glucose monitoring, other measurements taken at clinic visits provide an assessment of long term control over the previous month, as well as corroboration of values reported by patients. As stated above, a fasting blood glucose determination is usually sufficient for non insulin treated patients, but is of limited value for type I patients due to the common high day to day variability.

The measurement of glycosylated haemoglobin (HbA_{1c}) is widely accepted as an objective and quantitative index of blood glucose levels during the preceding six to ten weeks[1]. The aim of

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[1]For biochemists: an explanation why glycosylated haemoglobin is important seems appropriate at this stage. Haemoglobin may be separated by cation exchange chromatography into nine components: HbA_0 HbA_{1a1} HbA_{1a2} HbA_{1b} HbA_{1c} HbA_{1d} HbA_{1e} HbA_2 and HbF. Normally, 90% or more is HbA_0 and between 4 and 6% is HbA_{1c} (glycosylated haemoglobin); these are the two most abundant species. However, HbA_{1c} is increased in diabetes due to the

therapy is to obtain a near normal value of HbA_{1c} (<6.1%) but in type I diabetics a more realistic aim is an HbA_{1c} of less than 10%. The problem with this assessment of long term control is that it indicates mean glucose levels, but gives no idea of the variability; a patient with a HbA_{1c} of 6% may appear to be well controlled but blood glucoses may be highly variable, between say 2 and 20 mmol/l. There is also variation in the average (120 day) life cycle of the red blood cells between patients and the cells' permeability to free glucose. Therefore, HbA_{1c} should be interpreted with caution.

Other proteins are also glycosylated non-enzymatically (e.g. albumin and plasma protein), and may respond more quickly to changes in overall glycaemia, but further research of these measurements is required before they may take their place beside Haemoglobin A_{1c} as indices of long term control.

Nathan et al (1984) evaluated the clinical information value of HbA_{1c} by comparing it to practitioners' estimates of glucose control over the preceding 10 weeks. He concluded that the HbA_{1c} assay provides information about the degree of long-term glucose control that is not otherwise obtainable in the usual clinical setting. The linear regression equation for mean glucose (MBG) in mg/dl from HbA_{1c} (in %) obtained in this way was:

$$MBG = 33.3\ (HbA_{1c}) - 86 \qquad (r^2 = 0.92, r = 0.958). \qquad (E1.3)$$

As well as the correlation to mean glucose value, HbA_{1c} may be a good indication of the level of microangiopathic changes responsible for diabetic complications, especially retinopathy and nephropathy. It is thought that thickening of basement capillary membranes may be a contributory factor in these complications, and this thickening occurs by the same type of mechanisms as the formation of HbA_{1c} described above.

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formation of a stable ketoamine from an aldimine adduct of glucose and the terminal valine of the beta chain of the haemoglobin, a direct result of excess blood glucose levels.

Diet

Food is made up of four major dietary constituents: carbohydrates, fats, protein and dietary fibre. Carbohydrates have the greatest effect on the blood glucose and, in the past, diets have been recommended that were low in carbohydrate content. Current opinion is the opposite however: fats should be restricted to less than 30% of the calorie intake, with as much as 50% of calorie requirements coming from carbohydrates. Some simple, sweet sugars are allowed but most of the carbohydrates should be from complex starches, such as those contained in potatoes, rice or bread. Complex carbohydrates are metabolised more gradually and therefore do not produce sharp glucose "peaks", the gradual absorption also helps to prevent hypoglycaemia. Another consideration is the minimisation of risk factors involved in other illnesses, particularly heart disease. It is recommended that protein intake should also not be excessive due to the increased risks of kidney disease in diabetics.

Many newly diagnosed overweight type II diabetics may delay the progress of the disease by losing weight. Patients see a specialist dietician for education concerning how to adjust their diet, and reduce calorie intake, while maintaining a balanced diet. They may be given a list of foods to eat, which should help them to reduce their weight. This should reduce the strain on their body's own insulin production mechanism, so that they may then produce enough insulin to meet their own requirements, and no biochemical treatment is required. Regular exercise is also desirable, as is the case for the general population. The WHO recommends a minimum of two hours per day of mild exercise for all diabetics (Lean and James 1986).

Regular lipid measurements (triglycerides and cholesterol) should be carried out on all diabetics, and dietary advice given accordingly. Early indications of long term trials indicate that due to increased cardiovascular risk factors with diabetes, smoking, obesity and hypertension should be reduced if possible.

A change in dietary habits may be all that is required to control type II diabetes, in which case patients are said to be following "diet therapy". In non-ketotic, overweight patients diet therapy is always given a trial period before drug intervention.

Oral Hypoglycaemic Therapy

When diet therapy is unsuccessful further treatment becomes necessary. Oral agents were first put into widespread use in 1957 in the form of sulphonylureas. Sulphonylurea drugs act by stimulating an increased release of insulin by the pancreas, and therefore require the patient to have some functioning beta cells. Sulphonylurea tablets may therefore be used only in the treatment of type II diabetes.

The first sulphonylurea to be used was Tolbutamide. This was later followed by Chlorpropamide which was five times as effective as Tolbutamide in increasing insulin production due to its chlorinated form. More potent drugs followed; they included Glibenclamide, Glipizide and similar types; these later sulphonylureas generally had a shorter duration of action and some have to be taken twice daily.

A second group of oral hypoglycaemic agents are the biguanides; the only commercially available biguanide in the UK is metformin; phenformin was withdrawn in the 1980s because of the high incidence of lactic acidosis among patients while they were taking the drug. It is not known precisely how biguanides work to reduce blood glucose, but one theory is that they work to enhance the utilisation of glucose by a different method than insulin (Klip and Leiter 1990). Metformin must not be used in renal or hepatic dysfunction because of the risk of lactic acidosis.

As weight loss is a primary therapeutic aim with many people with type II diabetes, new tablets which aid diet are gaining in popularity. One example is dexfenfluramine (Willey et al 1991); it is a seratonin antagonist and may be of use when metformin is contraindicated, as many physicians suspect that sulphonylurea and insulin cause weight gain. The evidence of the UKPDS study does not back this suspicion however. A three year random study with diet,

sulphonylurea or insulin therapy in 1592 type II diabetic patients showed equal efficacy of Chlorpropamide, Glibenclamide and insulin in reducing blood glucose and HbA1c, with no significant extra weight gain over the group treated with diet alone. Based on these findings, drugs which are designated as weight reducing agents are not included in the present work and will not be considered further.

Insulin Replacement Therapy

Insulin replacement therapy has gradually evolved ever since the insulin hormone was first isolated in 1921. Lack of control over the action of injected insulin has always been a problem when compared to physiological control mechanisms. The first insulin preparations developed were absorbed quite quickly and had to be injected two or more times per day. Researchers striving to mimic the physiological profile of insulin production mixed the acid insulin molecule with protamine and then zinc to produce insulin formulations with slow absorption rates to cover the basal insulin requirements. Renner (1985) describes the evolution of insulin therapy; from the first subcutaneous injections made by Banting and Best in 1922, through experiments with continuous intravenous infusion in the mid 1970s, to the routine use of continuous subcutaneous insulin infusion pumps (CSII) which began in 1977.

Renner has listed seven basic rules for subcutaneous insulin replacement therapy (table 1.3) (Renner 1985). These basic rules provide important principles although they do not in general correspond to the classic rule definition used in decision support system terminology. They would perhaps better be termed axioms of insulin replacement therapy. More specific rules of insulin adjustment for specific insulin types and regimens were required.

Table 1.3 Basic rules for subcutaneous insulin replacement therapy

1. The number of injections should increase with degree of instability,
2. The duration of action depends on the amount of injected hormone,
3. Regard should be taken of the existence of circadian rhythm of insulin requirement,
4. Day-to-day variation depends on the type of insulin,
5. The later the night-time injection the less the hypoglycaemic risk,
6. The amount of regular insulin should be increased with degree of obesity,
7. Patients should use the same area of injection at the same time of day in order to reduce absorption variability.

Evolution of insulin formulations followed a gradual progression as the severity of long term diabetic complications became apparent once life was preserved. The insulin isolated in 1922 was called regular insulin; the duration of action of the injected regular insulin was (and still is) between 6 and 8 hours, and the peak of activity is much later than in normal physiological insulin secretion (fig 1.1). Injected insulin peaks at about 40 minutes after an injection, regardless of food intake, whereas normal insulin production peaks at about 10 minutes after a meal begins. In 1926, the first crystallisation of insulin was carried out, and in 1934 crystallisation in the presence of zinc prolonged the action of insulin to over 12 hours, thus cutting down the number of injections to two per day. In 1936, protamine insulin was formed, which prolonged the duration to over 24 hours; these longer acting insulin formulations were given the name ultralente.

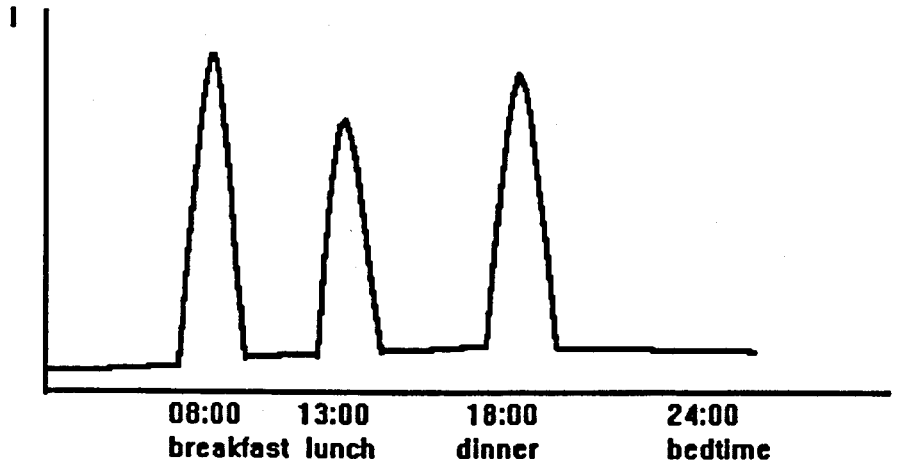

Fig 1.1 Physiological insulin release profile

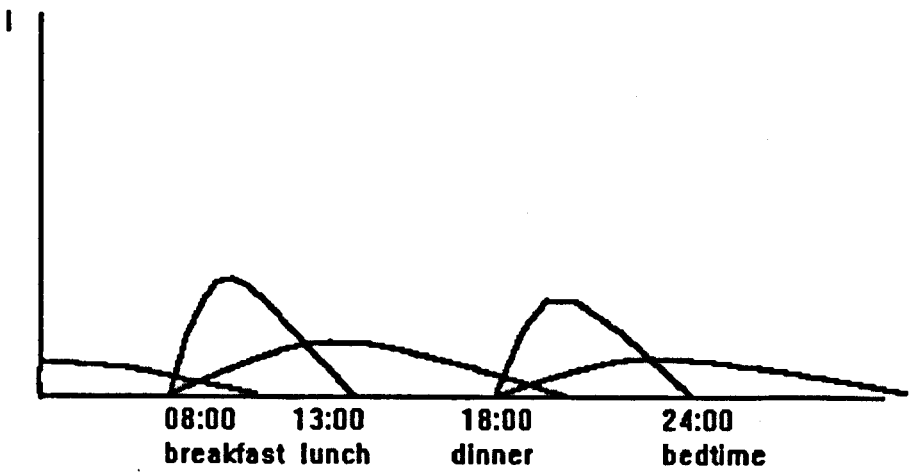

Fig 1.2 The soluble isophane regimen: idealised profile

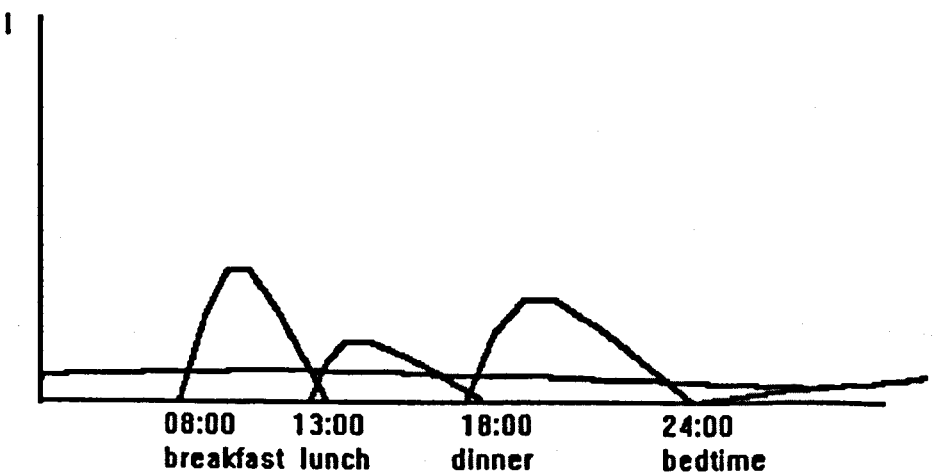

Fig 1.3 The basal prandial regimen: idealised profile

In order to eliminate the need for mixing of insulin crystals to form a dilution, zinc crystals in suspension were created in 1951. There were many problems with insulin allergies and impurities due to the use of unpurified beef and porcine insulins, but in 1973 purification procedures provided much purer single peak insulin by gel chromatography. Then, in 1982, semisynthetic human insulin, followed in 1983 by biosynthetic human insulin, became available due to processes of enzymatic modification of porcine insulin (emp), or by recombinant DNA biosynthesis (prb).

With the use of insulin comes an increased need for dietary care. The dietician should be considered an integral part of the health care team for all diabetics, and regular consultation (at least once per year) is advised by diabetes authorities such as the ADA (American Diabetes Association, ADA consensus statement 1990). The dietician should try to educate patients in general principles of nutrition, how best to avoid complications, and most importantly, how to balance insulin and carbohydrate intake to avoid hypoglycaemia.

Insulin Regimen.

In order to explain the basis of Renner's axioms and to see how they may be applied in practice a closer look needs to be taken at the available insulin formulations and how they combine into the various common insulin regimens.

As shown in fig 1.1 physiological insulin requirements for normal metabolism consist of an underlying continuous basal need with extra requirements superimposed to cover meals. The basic aim of insulin replacement therapy is to mimic the physiological profile, the axioms of Renner do not mention this matching nor any relation to diet and exercise.

Although there are over thirty different insulin formulations (Chadwick 1991) they may be categorised into four main types. The categorisation depends solely on the duration of action of the injection, which in turn depends on the manufacturing process. The effect on duration of action of the size of a dose is more minor (axiom 2) and may be overlooked in practice. Short acting, intermediate acting and long acting insulin are the three simple types whilst the fourth

type of insulin is a mixture of two of the basic types and is termed mixed insulin. To illustrate the confusion in terminology and lack of standardisation there are thirteen common synonyms for short acting insulin; those in common usage include: soluble insulin, regular insulin and clear insulin (Chadwick 1991).

The most commonly prescribed insulin regimen consists of short acting and intermediate acting insulin. The regimen is popularly known by the name "soluble isophane" after the two types of insulin traditionally used.

As is the case with all regimens which include soluble (short acting) insulin, the short acting insulin is given to cover meals (i.e. pre-prandially), either before all three main meals or just before breakfast and the evening meal. This follows from Renner's first general principle as the midday injection is only prescribed if pre-evening meal glucose test results are unstable.

It can be seen from fig 1.2 that the combination of short acting and intermediate acting insulin given twice per day bears little resemblance to physiological insulin secretion (fig 1.1); however, its careful combination with diet and exercise has resulted in successful control for many patients for a very long period of time, (some for over 50 years) and its continued use can therefore be justified.

The majority of mixed insulin formulations have a proportion of short acting and a proportion of intermediate acting insulin; for example 30% short and 70% intermediate. These insulin types are suitable for stable patients and those for whom intensified therapy is not appropriate. Adjustment of one type of insulin is made by changing the prescription to a different mixture. Adjustment of the dose must be based on a need to change both insulin types by the same proportion.

A regimen which more closely mimics physiological secretion is the basal prandial regimen (fig 1.3). The basal requirements are met by a single daily injection of a long acting (ultralente) insulin while meals are covered individually by short acting insulin as with the above regimen. Often, two short acting doses - one at breakfast and one before the evening meal - are sufficient

to provide adequate control as the duration of action of short acting insulin covers the midday meal requirements. The option of a third dose at midday is used for those who eat a large meal at that time or for people who are more sensitive to variations in insulin and glucose levels.

Some people refer to the two dose regimen as "conventional" therapy and the second, three dose regimen as "intensified" or "multiple subcutaneous injection" (MSI) therapy. Why a distinction needs to be made over one extra injection at midday is unclear, especially with the introduction of simple insulin "jet" devices (Novopen, Accupen) for easy, discrete one-handed injection. Patient acceptability of multiple injections is high, especially in newly diagnosed adolescents (Tubiana-Rufi et al 1989). In fact, in comparison with continuous subcutaneous insulin infusion (CSII) therapy the inconvenience of a midday injection is minor.

Variations on the basic basal prandial regimen include the option to split the ultralente dose; equal amounts of long acting insulin are taken before breakfast and before the evening meal; this may reduce variability in circulating insulin through the day and thus produce a more stable basal level of blood glucose. Normally the long acting dose should be given at bedtime so that any perceived peak of action occurring at about 6-8 hours should counteract the early morning rise in blood glucose associated with the dawn effect. This is in accord with axiom 5 of table 1.3.

Alternatives to Injected Insulin

Insulin injections are unpleasant to do and alternatives which are less painful, more socially acceptable and produce better blood glucose control are actively being sought. The problem of matching insulin supply to the body's variable demand has lead to the development of insulin infusion devices, commonly known as insulin pumps. Pumps may be external to the body or surgically implanted, usually in the chest cavity. The first implantable pumps appeared in 1981, with developments of the artificial endocrine pancreas or Biostator first described by Albisser (Albisser et al 1974). However, the possibility of feedback-controlled, long term infusion of insulin has not found wide-spread physician or patient acceptance due to high risks of mechanical breakdown, infection and inconvenience. Less than 1% of diabetic patients have

used an insulin pump at any time. The vast majority of patients do not want the inconvenience of wearing such a device as a constant reminder of their diabetes. Even with pump treatment, the response to rising blood glucose at meal times is insufficient to produce a close approximation to normal physiological insulin response. Many problems exist with so called closed loop pump systems which have implanted glucose sensors, and it will be a long time (if ever) before such systems are in widespread use although their use in some hospital settings has been successful (Kernstine et al 1987).

Nasal insulins are also under development. The nasal route has the benefit of extremely quick absorption, but suffers from problems of variable absorption rates, and nasal irritation problems. Only around 10% of nasal insulin is absorbed, which necessitates very high doses, which in itself is probably not a problem. Patients are very enthusiastic about nasal insulin use and consider it much more acceptable than injections (Holman and Steemson 1991). The problems of dose titration multiply with the use of nasal insulin due to the increased amount of applications required to provide complete cover for meals and snacks. Alternatively, patients will not need to be so regimented in their diet.

Pancreas transplants are rare and expensive; they are normally only carried out at the same time as kidney transplants. Recent interest has developed in transplanting only the insulin producing pancreatic islet cells. However, the operation is far from perfection and will not become common for some time yet. The major problem is the autoimmune destruction of the newly implanted cells. A possibility to overcome rejection is the use of hybrid devices, which have an artificial semi-permeable membrane; this membrane lets glucose and insulin through, but not the islet cell antibodies (ICAs) (Friedman 1989, Sarver and Fournier 1990)

It is obvious that these new developments have problems and are unlikely to become widespread and accepted within the next few years. Instead, intensified conventional therapy with multiple injections of different insulin formulations has proved the test of time as the "treatment of choice" (a remark attributed to Banting himself) and for some time to come, daily

(multiple) insulin injections will continue to be the only reliable safe means of treatment. Long overdue optimisation of this method is therefore of vital importance.

Hypoglycaemia

As implied in the earlier discussion, insulin, once injected, raises plasma insulin levels for a long period of time, during which there is little that patients can do to reduce the level. If there is no free glucose in the blood due to ingested carbohydrate, the insulin will work on the normal amounts of glucose present in the blood; this causes a glucose shortage and leads to a condition known as hypoglycaemia. Hypoglycaemia may cause several unpleasant side effects such as sweating, dizziness, hunger, trembling and finally loss of consciousness as the brain is starved of glucose. The brain is particularly sensitive to low glucose levels as it cannot obtain energy from many other sources, as other organs do, due to its blood-brain barrier. Other energy sources in the blood, except for the ketone bodies, have molecules which are too large to be transmitted to the brain.

It is vital that diabetics learn to recognise the earliest symptoms of hypoglycaemia and act to counteract them and prevent deterioration into an unconscious state. Mild neuroglycopenia, which occurs at blood glucose levels less than 3 mmol/l, produces subtle intellectual and psychomotor impairment; severe neuroglycopenia, which is defined by blood glucose levels less than 1 mmol/l, causes confusion, disturbed behaviour, fits and, ultimately, unconsciousness. Permanent brain damage is unlikely after severe hypoglycaemia, although the chance is increased after excessive alcohol intake. In addition, generalised autonomic activation is triggered by blood glucose levels less than 2 mmol/l. This causes tremor, tachycardia, sweating, altered salivation and hunger. There are thus two distinct mechanisms by which warning signals may be detected by patients in the body.

Some patients have reported loss of awareness of hypoglycaemia, this may be due to autonomic neuropathy, or the effect of intensified insulin therapy. This "unawareness" is often reported after a transfer from animal- based insulin formulations to synthetic human insulins; this is probably due to pharmacokinetic differences or lack of care in prescription practice. However,

Patrick et al (1991) found that when hypoglycaemia was induced in seven patients by intravenous infusion of both human and animal-based insulin types there was no significant difference in autonomic reaction; the debate continues. In contrast, for some patients the classic symptoms of hypoglycaemia may occur at relatively normal blood glucose levels. This may be due to a sudden decrease in glucose level from hyperglycaemia, or it may be due to an altered threshold of perception of symptoms, related to a reduced rate of transport of glucose across the blood-brain barrier. For this reason, it is advisable for patients who detect hypoglycaemic symptoms to measure actual blood glucose, if possible, so that physicians can assess target blood glucose levels in the light of the increased threshold of hypoglycaemia.

Alleviation of hypoglycaemic symptoms is usually easily achieved by the ingestion of glucose, either special glucose tablets or a food containing simple sugar. Sugar takes longer to have an effect as it requires hydrolysis to yield glucose so the response would be slightly slower to sugar than to pure glucose; however, this is often not important unless the onset is particularly acute. Recovery from hypoglycaemia depends on glucose counter-regulation by catabolic hormones: glucagon, adrenalin, cortisol, growth hormone and vasopressin. It may be delayed in long-standing diabetes, or by beta-adrenergic blockade. Sulphonylurea may also cause hypoglycaemia, and is particular dangerous in long acting tablets such as Chlorpropamide, which is therefore contraindicated in the elderly. Treatment of serious prolonged hypoglycaemia may be by an intramuscular injection of glucagon or intravenous glucose infusion may also be required for prolonged hypoglycaemia due to long acting sulphonylureas.

Low blood glucose can be brought about by several means, such as extra exercise which uses up the available glucose in the muscles, or due to a low carbohydrate meal which does not provide the glucose in the first place. If hypoglycaemia occurs with no apparent explanation, then insulin doses should be altered to avoid a repetition of the event the next day. While low blood glucose, in itself, is not thought to be dangerous in the long term, a bad hypoglycaemic reaction which occurs without warning while a patient is driving may become instantly fatal. It is for this reason that people with diabetes mellitus are obliged under the Road Traffic Act 1974

to report their diabetes to the licensing authority (Saunders 1992). In the UK, people who use insulin are not permitted to hold Heavy Goods Vehicle or Public Service Vehicle licences.

Statistics show that hypoglycaemia is responsible for 3-4% of total deaths related to type I diabetes; over 30% of type I patients experience hypoglycaemic coma in their lifetime and around 10% go into coma once per year. It is estimated that about three percent of patients are incapacitated by regular, severe hypoglycaemia. It is thought that a great number of these consequences could be reduced by improved patient knowledge and improved insulin adjustment decisions.

CONCLUSION

It should be apparent from this review that proper management of diabetes patients is important, difficult and expensive. In developed countries the cost of diabetic health care may be estimated at between 4 and 5% of total health care costs (Williams 1991) There is, therefore, much pressure for effective management. In many cases resources are stretched, so that a policy of damage limitation is followed which is less than optimal. The computer systems developed for this thesis, once they are more widely validated and tested, could provide decision support for optimal diabetic management. This thesis demonstrates that the systems could well lead to a reduction in the real costs of the disease as well as an improvement to the quality of life of patients.

Patients should benefit from more freedom of lifestyle, and a better understanding of their diabetes, from the use of the hand-held system POIRO. Physicians ought to benefit from therapy adjustment suggestions, and especially insulin dose alterations suggested by the PRESTO system.

CHAPTER 2 - COMPUTER AIDS TO CLINICAL DECISIONS

INTRODUCTION

Medicine has provided the domain for much of the early research and development of intelligent decision aids. Enthusiasm for the introduction of computerised clinical decision aids into practice has, however, been minimal. Medical problems which are appropriate for intelligent computer decision support technology include diagnosis, and therapy decision making. Many diagnostic systems have proved to be successful, at least at the research stage, although none have since moved on to general, widespread use. Even less progress has been made in therapeutic decision support systems. This could be due to problems with validation and evaluation of the systems, as well as purely technical problems concerned with the use of computers in everyday medical practice. One possibility why diagnosis has been the major focal point of development is its relatively narrow goal - a single desired outcome, and the clear criteria for reaching that outcome. There is much more agreement on the correctness of diagnosis than exist in decisions as to the best course of treatment to take.

In this chapter, medical decision aids are examined from three perspectives. First, the physician's views and desires are described in relation to previous research in the area. Second, the computer scientist's perspective is examined with reference to system design and development. Finally, examples of current research systems are given. Items of specific relevance to the research carried out for this thesis are detailed within the text as appropriate.

Physicians Acceptance of Decision Support Systems

The first problem to be overcome by any computerised decision support system is the general apprehension of physicians towards computers (Osborne et al 1992). The problem appears to be worse in junior doctors (Moidu and Wigertz 1987). However, this is a wider issue and may be solved in time perhaps by changes in the availability of medical informatics education.

Seven recurring questions arise from physicians about medical decision support systems (table 2.1).

Table 2.1 Common questions from physicians (Shortliffe 1980)

1) Is it reliable?
2) Do I need it?
3) Is it easy to use?
4) Does it help, without being dogmatic?
5) Does it justify itself with sufficient explanation?
6) Does it fit into my daily routine?
7) Is it designed to make me feel comfortable when I use it?

Reliability may be categorised into physical (or hardware) reliability and decision (or software) reliability. Physical reliability has improved as faster and more reliable components have become available. Quantitative estimates of reliability can now be given in terms for example of the mean time between failures. Acceptance criteria for reliability are related to risk and safety considerations, and standards are currently under review (Bennett 1991).

Software reliability is different to hardware reliability, in that faults are made in the design process rather than during production or due to degradation with time. Therefore, software reliability can be improved by good programming design practices. Conventional software testing, based on functional requirements, has been the only assurance of correct operation of a program. However, such testing cannot be guaranteed to locate faults, which often materialise much later in deployment. New standards place much emphasis on formal mathematical methods for software testing, in particular by the definition of formal specification languages such as the" Z" notation (Spivey 1988). Such formal methods of development should increase the soundness of safety-critical systems but are not a panacea. Formal methods considerably increase overheads and their use was not thought appropriate for the development carried out in this research. Instead, the software development used standard software engineering development practice with special attention to rigorous testing by way of simulation studies and test cases selected to check built-in safety features (such as a limitation in insulin dose adjustment - see chapter 4).

Physicians must make up their own mind whether or not they need a decision support system and the considerations of the previous section will be affect this decision. It is, however, well documented that physicians often experience indecision (Rector ibid.) which would appear to indicate a need exists, whether it is admitted or not.

Ease of use depends on the user interface and the underlying design of the information-gathering modules. Medical consultations often appear to be unstructured, the order of questioning dynamic and chaotic. Some researchers have put forward the idea of a user model, which adapts the system to individual users. A review of models of users is given in Green, Schiele and Paine (1988), the most useful of which are those of Card et al (1983). The present research has shown that the triggers which promote a particular line of questions within a consultation are not well defined and will probably differ between patients as well as between clinicians; therefore, it may be better to avoid trying to develop a user model, but to provide a logical, easy to use framework and help the user to adapt to the framework. User models are not, in any way, used in POIRO or PRESTO, but a future version of PRESTO could examine the use of such models if desired.

A special case may be made for the use of user models for on-line help (Gwei and Foxley 1990) in order to match help to user's needs and experience; this categorisation presents more appropriate information in context. A discussion of the critical role of display, especially menu systems, can be found in Howes and Paine (1990). Interfaces to help systems can be improved, it may be possible in the future to give users freedom to use natural language by appropriate implementation of parsing and natural language understanding.

Once physicians are happy with how to use the system, the actual usefulness of the system comes under scrutiny. The level of decision support which a system provides depends on the needs of the physician concerned. The advice offered should be in terms of support. Dogmatic, prescriptive advice will not be acceptable to many physicians. The possibility of two-way dialogue between the system and the user is attractive and would provide mechanisms for a

consensus opinion to be formed. In particular, users may want to offer consideration of an alternative to the choice offered by the system. The importance of a user model in these circumstances is in knowing what kinds of decision support are required. For instance, where there is a choice of therapeutic options, whether the physician or patient has any personal preference for one over any others. Systems should be flexible, and be able to respond constructively to suggested alternatives from the user, much like experts would to a junior questioner.

Explanation facilities have improved from the early systems' facilities for presentation of encoded rules as they were used. The use of symbolic development languages which closely resemble natural language is attractive in that rules may be used as sources for pseudo-natural language explanations. Explanations which are genuinely built up from natural language will probably be developed within the next ten years but, for the moment, the "state of the art" in explanation is the presentation of prepared text when called upon by the user. Because of this, explanation in many knowledge bases is little more than justification; for really useful explanations an interactive dialogue has to be entered into, so that the user can prompt the level of the explanation given. Current explanation facilities have been little more than justifications of the results, without actually explaining the reasoning, or how to use the advice given. Explanation is central to the acceptability of decision support systems. Recommendations must be backed up by sound lines of reasoning. It is recommended that true explanation includes causal links to suggestions and the deeper, underlying knowledge. Current efforts into natural language explanation centre on intelligent use of semantic links between decision entities (Crook 1992).

Many physicians now use computers in their daily routine, the number of computers in British general practice for instance has risen steadily and the majority of GPs now own a computer to help with patient administration and sometimes practical jobs such as prescription printing. The problems with decision support systems fitting into the daily routine include mechanical, epistemological and psychological problems; all these have to be overcome in some way.

Mechanical problems include ease of use, speed and, for some applications the size of the system. Memory capabilities are, however, improving and larger practices are using networks for sharing of patient data. Physicians want to expend as little effort as possible on data entry, and they require fast responses in real time.

The human computer interface (or HCI), has a central and vital role in the success of any computer system. Thimbleby has suggested (Thimbleby 1990) that much more attention should be paid to the development of user interfaces, especially for non-specialists in critical situations. He describes the user interface in terms of scientific research, and suggests outlines for developing help systems. In doing so he describes the types of user and types of errors which are commonly made by users and which HCI design should attempt to minimise or ideally eliminate completely if possible.

Epistemological problems concern the depth and representation of knowledge within a system. The quality of decisions and explanations is highly relevant to the study of knowledge representation, and techniques of inference used. A major problem with many medical decision support systems is the amount of background medical knowledge required outside of the specific field of the system. The need for help, in diagnostic systems especially, is often with the difficult, non standard problems which often involve multiple pathology. This is less of a problem in a limited and well circumscribed domain such as insulin adjustment, or even general diabetes management.

Medical classification is not a scientific, well ordered system, as is biological taxonomy for example. This also causes problems with storage and transfer of data, as well as problems with terminology in language understanding. Medicine has been described as a vestally complex domain (Groen and Patel 1988), unlike chess or physics for example. It is inconsistent with the paradigm of pattern recognition and forward reasoning which is often associated with it. In medical domains, comprehension is the perceptive process most commonly ascribed to expertise. The theory has been put forward that medicine is essentially a backward reasoning

process, akin to the hypothetico-deductive process often advocated as a paradigm of scientific reasoning. The knowledge of medicine may be decomposed into underlying units of meaning, known as propositions; this fits in well with the use of rule-based logic and symbolic reasoning.

Psychological studies show that many physicians experience technical phobia with respect to computer technology. How physicians react to the system will depend on their general attitude to computers as well as their consideration of the above criteria. Some physicians may feel threatened by a computer, while others may be deeply distrustful of its decisions, especially if the decisions do not agree with their intuition.

Consideration of the ethics of computer decision making systems have led to a redefinition of the roles of patients and health care professionals; the patient is generally the ultimate decision maker, unless totally incapacitated by the medical condition; physicians and other health care professionals attend the patient and may utilise the decision support system as a tool. Even the most sophisticated of tools cannot be assigned the status of a moral agent, and the consequences of the medical decision must be borne by the patient and the physician. There can be no place for ascribing bad decisions to computer error; computers should only improve decision making power. The medico-legal issue of liability is equivocal with regard to developers of intelligent decision system; the designers of the system may be liable for bad decisions, unless careful attention is paid to warnings and disclaimers within the program. A more interesting question is whether a physician could be liable for not using an available system to help with decisions. These ethical questions are, however, beyond the scope of this thesis.

EVOLUTION OF COMPUTERISED CLINICAL DECISION SUPPORT

There have been several phases in the development of computerised clinical decision support tools. The first application of computers was the development of computer-based medical records. The requirements of medical databases are to store diverse information such as medical history, physical examination findings and laboratory data. One of the first systems to

address the acquisition of medical history was the Plato I system (Slack 1966). Two principles of medical databases were introduced at this time: (1) that reliable and manageable clinical databases are necessary for the construction and validation of decision systems. (2) Data acquisition systems should be capable of admitting and interpreting data from physicians according to their general style efficiently and quickly. Slack later developed the art of data acquisition to a system for acquisition of data directly from patients and thus produced the first clinical patient-oriented decision support system.

Hospital information systems (HIS), such as the PROMIS system (Weed 1978) produced great clinical interest but still did not make the breakthrough into acceptable everyday use. The major reason for this lack of acceptance appears to have been the one-way nature of the interaction. Physicians were expected to enter a great deal of information (complete medical case histories in fact) for virtually no return. It became apparent at this time that the goal of adapting the user interface to accept direct uninterpreted and unstructured data from clinicians was impossible and time would be spent more profitably on the generation of decision support from a smaller set of abstracted data.

A solution to the nomenclature problem could be a standardisation of medical terminology, with extensions to allow for the use of synonyms locally. This may be achieved by the use of a classification or coding system. The International Classification of Diseases has produced such a system, the current version is termed ICD-9, but improvements are expected in ICD-10, due within the next year. In the UK, the definition of the Read clinical classification system, or Read codes as they are generally known, has provided a reasonably thorough basis for the complete encoding of medical knowledge (Read and Benson 1986). However, the classification has its limitations, especially with the representation of events and the abstraction of clinically significant features in a certain context. However, the Read codes are fast becoming the medical dictionary standard in British hospitals and general practice and the next version of the codes (version 6) should improve on its deficiencies in version 5. The Read

codes already have the advantage that they subsume other international coding systems such as ICD-9 and are compatible with the use of other coding systems.

Clinical databases and hierarchical classification systems fall into what may be called supporting sub-systems. They are essential for storage of clinical data and provide support for systems which actually generate decisions and decision support for the physician. The type of real support required by physicians may be one or more of the following functions: reminders of adverse drug reactions and interactions, clinical diagnostic and management support, mechanisms to promote patient compliance with therapy. The last of these is perhaps the most revolutionary and important development in recent years. Patients who use portable, hand-held or pocket computers to manage a medical condition have the benefits of a clinical advisor "on call" 24 hours per day. The collection of data permitted by these new systems also provides a service to the epidemiologist, who in some cases will be able to collect data which it had previously been impossible to obtain.

Intelligent Decision Support: Expert Systems.

There have been several definitions and classifications of expert systems (ESs) and intelligent decision support systems (DSSs), (Ginzberg et al 1982). In the first phase of development of DSSs, systems were labour-intensive, in that the user had to define what alternatives were on offer. In the 1960s, early decision systems merely permitted the user to extend his own decision making capabilities by data collection, manipulation and representation. These early systems used probabilities supplied by the system user to estimate a best course of action. The next major development in computer systems was the introduction of spreadsheets. Spreadsheet technology belongs to a particular set of decision support systems (Sprague and Watson 1986). A major deficiency of spreadsheets is the lack of a system for formation of hypotheses. In their present form, spreadsheets offer extremely powerful data manipulation and statistical estimation capabilities, but at least some level of computer skill is required to use the systems, and they may be limited in their support for different methods of data entry.

Intelligent hypothesis formation was seen as a desirable addition for the development of IDSSs. Some other essential criteria are listed below.

Table 2.2 Essential criteria for DSS

Supports but does not replace decision making
Directed toward semi-structured and/or unstructured decision making tasks.
Data and models organised around the decisions.
Ability to carry out interactive processing
User determines DSS control
DSS should be adaptable to changes in teh environment and decision maker's style.
Easy to use software interface.

Early AI research centred on general problem solving methodologies (GPS). The theory was that a generalised set of problem solving methods, which included various search algorithms, would be capable of application to any specific problem. This was not the case and it soon became clear that a more fruitful approach is to provide the computer with a substantial amount of very specific data on a single area, or domain. The data, or knowledge, was usually supplied by an expert in the chosen domain and elicited by a human questioner, called a "knowledge engineer", who later converted the information into a suitable format for the computer. This move showed that computers could be made to reason about complex and very specific domains in a sensible and useful way.

Medical applications were at the forefront of the new developments, called expert systems due to their ability to act as experts in a single domain. The most successful and famous of these systems was MYCIN (Shortliffe 1976). Knowledge was entered into the system in the form of "if- then-" constructions known as "production rules", these type of systems are called "rule-based". Although extremely successful at predicting correct diagnoses, it soon became clear that the methods employed in MYCIN were not sufficient to model decision making processes of domain experts, nor to extend to other domains. This came to light with the requirement for quality explanations of the reasoning processes, and for the application of the knowledge-based systems to teaching problems.

NEOMYCIN (Clancey 1988) was specifically developed as an intelligent teaching aid. Unlike its precursor, MYCIN, the knowledge within NEOMYCIN is structured in a rich hierarchy of facts, findings and hypotheses. The reasoning processes are independent of the domain specific knowledge. The knowledge base and reasoning procedure thus constitute a model of human knowledge organisation and diagnostic reasoning. Further refinements produced expert system "shells" to which EMYCIN (Shortliffe 1980) could be said to belong. These shells where developed in such a way that the reasoning capabilities were completely separated from the domain-specific knowledge and it was this separation that produced a huge increase in interest in more general AI problems again.

A return to more general representation and reasoning techniques followed. AI theory developed into a "proper" scientific discipline with the development of theories for logic programming, the logic languages Prolog and Lisp provided foundations for a number of systems. Theoretical contributions concerning decision making, temporal and other non-standard logics have also been addressed and in the process some psychology and cognitive science findings have been incorporated into AI research. The main focus remains the development of sophisticated and easy to use decision support systems, with medicine at the front of the queue for useful systems.

DESIGN OF AN INTELLIGENT MEDICAL COMPUTER SYSTEM

The following sections describe, in general terms, the processes involved in building an intelligent decision support system, particularly in the field of medicine. It is by no means an exhaustive catalogue of techniques, but is taken as an outline of the type of methods which were influential in the eventual choice taken for the project. The classical waterfall model of development such as recommended for all software engineering (Sommerville 1989) is assumed, the overall methodology can thus best be described as an incremental prototyping approach where the system design was refined with reference to prototype developments.

Definition of Requirements of the Problem

The first stage in solving any problem is to state what the problem is in general terms and to determine what levels of decision support are required. First, is the problem well structured? If it is well understood and well structured then algorithms may be defined and conventional programming techniques may be appropriate. If problems are ill defined and complex then some degree of uncertainty is present, and some of the concepts of AI programming introduced later are necessary.

How much detail is required? Is the problem well-bounded? Expert systems function most reliably when the domain is well-bounded and a relatively narrow field. Once the domain starts to widen, to cover more diverse situations, multiple experts have to become involved. This creates problems of expert knowledge conflict which have to be resolved in some way. AI techniques are most useful when the normal (analytical) problem solving approach is unable to quantify all the necessary information. Suitable applications for AI methods usually contain at least some heuristics or uncertainty.

The original aim of any system will inevitably be updated as research progresses, either to a higher goal if progress is smooth, or scaled down if progress is slow. However, keeping the original aim in mind is important, so that the system designer does not get side-tracked into other areas. It is often desirable to rapidly prototype some domain knowledge, so that the domain expert can see some results for all the effort of knowledge acquisition.

Knowledge Acquisition.

Knowledge acquisition covers all forms of knowledge assimilation, this may come about in at least three distinct ways.

1) Direct elicitation of underlying concepts from a small number of experts (possibly only one),

2) by observation of instances of the problem to be solved and the solution methods used by

human experts,

3) from published protocols and literature.

Virtually all systems will, at some stage, involve knowledge elicitation sessions with a highly qualified expert in the field of interest. This leads to the acquisition of high level heuristics and the underlying "deep" knowledge associated with the problem. The task of the system designer is then to implement this knowledge in relation to real cases of interest. Even if many experts are employed for knowledge acquisition, it is very useful to have one expert to act in situations of conflict and to decide which of two conflicting theories is best. The person who carries out this role is often referred to in the literature as the Knowledge Tsar (Davies and Hakiel 1988).

The interview is usually regarded as the easiest knowledge elicitation method for both knowledge engineer and expert to carry out. In order for the interview to be fruitful it is desirable to structure an interview before consulting with the expert and to ask specific questions. The relationship between knowledge engineer and expert may become strained if questions are vague or repetitive. The interviewer (or knowledge engineer) should aim to extract the knowledge from the expert in as general a way as possible. Implementation of the knowledge is a separate problem and the advantages of eliciting knowledge in a "pure" form include the chance to abstract into many different forms. The selection of an appropriate method for representing the knowledge is an entirely different problem to the initial collection of the knowledge. For this reason, it has been suggested that knowledge engineering is best carried out by two people (Davies and Hakiel 1988), one elicits knowledge without reference to a particular format; the other person then converts that knowledge into a format suitable for the computer system and software chosen for the job. It is said that this method does not constrain the acquirer of the knowledge and the knowledge may then have a more natural structure. The disadvantage of the method is that the knowledge may not fit into any computer representation system without constant modifications.

Protocol analysis is the name often given to the process of observation of actual cases of problem solving; experts are often asked to describe and explain their reasoning techniques and why particular questions were asked (Kassirer and Gorry 1978). Protocol analysis is not recommended early on in the design cycle as specific cases are rarely representative of underlying concepts, and it is difficult if not impossible for the system designer to extract underlying concepts from these sessions. There is also no guarantee that all decisions of importance will occur. Protocol analysis is much more useful later, when the level of background knowledge is already at an advanced level. It is highly useful for evaluation and further elicitation of specific cases overlooked in the initial stages. Protocol analysis may also lead to "exception" rules for use in unusual circumstances.

Knowledge acquisition from literature is a common source of clarification of concepts; it also helps the knowledge engineer to use correct terminology when generating text output. The wealth of published literature on most aspects of medicine make it highly desirable for system designers to study the literature and, in consultation with the expert, include the latest research developments in the system. A possible explanation facility, at an extremely low level, may be to reference sources of knowledge so that interested users may follow up advice.

Recently, much interest has focused on more contrived methods of knowledge elicitation, for example card sorts and laddered grids. Card sorts and laddered grids are intended to reveal an expert's conceptual map of a domain. In a comparison by Burton et al (1990) it was shown that contrived methods fared well against more traditional methods of knowledge elicitation (i.e. interviews and protocol analysis) and, more importantly, that the knowledge gleaned is of a different type and often augments the traditional techniques. In knowledge acquisition a mixture of, for instance, protocol analysis and laddered grid may be almost twice as fruitful as either technique alone.

The interview and protocol analysis were the main methods used for knowledge acquisition in this work. Upon reflection, some contrived method, such as laddered grid might have been

advantageous at an early stage of the research but the methods were unknown to the researcher at that time.

Knowledge Representation

Methods of representing knowledge are central to artificial intelligence research. Two problems exist; one is representing knowledge in concepts, the other is actually representing the concepts in a computer. One problem should not influence the other, although in the real world the constraints of computer linguistics will be a constraining factor in the design.

Documentation of decision problems has traditionally been done using branched networks known as decision trees. This method of breaking down the ultimate goals into smaller sub-goals works well for small problems, with few interactive factors. However, as the complexity of the problem increases, the complexity of the diagram increases. The diagram is eventually more complicated to follow than the list of rules which underlie it. Clinical algorithms may be represented by flow charts (Margolis 1992). Flow charts have the advantage that the detail is restricted only to items of knowledge which are directly relevant at the decision points. In practice, a large amount of background knowledge is also necessary and the information contained in these charts is therefore too limited. Recommended standards for flow charts are now becoming defined (Margolis 1992) which should aid users to follow different algorithms and to compare them for suitability for a particular medical domain and problem. Flow charts are appropriate for the documentation of the insulin adjustment algorithms which underlie the POIRO and PRESTO systems; some examples are given in chapter four.

The process of knowledge representation may involve deciding on a knowledge representation system for an expert system, or merely a data structure for the storage of items of data in a more traditional computer program, for example record structures in Pascal. Flexibility and clarity of the data structures is important at this stage, as the cycle is likely to be repeated and the structures updated regularly.

One of the limitations of early systems was their lack of relational structure. In order to provide structure to the knowledge Minsky (1975) introduced the concept of frames. This representation system is based on prototypes, defaults, multiple perspectives and partial matching. A frame is a structure for representing a stereotypical situation or object. It may be thought of as a network of nodes and relations, top levels are fixed and invariant, lower nodes may have various interpretations and values and are termed slots.

Semantic networks were first introduced by Quillian (1968) as a model for natural language representation and soon gained in popularity as a representation system. The meaning of words is represented with the help of a graph composed of nodes, which refer to concepts linked together by various relationships, for example causal or temporal links. This allows hierarchical structures to be built up and one of the most common uses is in building structures with "a kind of" or "is a" as the link. Symbolic reasoning and semantic networks are inextricably linked and the decision of which semantics, or ontology, to use for knowledge bases is one of the hardest tasks of knowledge engineering.

Whilst flowcharts provide a natural way to represent the algorithmic sections of the work in this thesis, their use is not always appropriate to represent other knowledge such as the knowledge used to construct the system's rules. A simple but effective approach to presenting the knowledge encoded in rules for the reader is a system known as indented knowledge structure (IKS) tables. The term is not (as far as I am aware) a standard term in AI, and the idea of representing high level knowledge in a relevance table with just one simple link (depends on) is also quite novel. An example is given in table 2.3 below.

Table 2.3 An example indented knowledge structure table

Result of examination depends on
- knee jerk
- ankle jerk
- toe sensation sensitivity

The advantages of IKS tables are simplicity, ability to organise data quickly and simplicity of expansion of any part of the knowledge. The knowledge is declared in natural language rather than coded by letters and symbols. The single link in the knowledge structure is the clause "depends on", and hierarchical knowledge structures may be quickly defined with these tables. The refinement of the knowledge into different link types with different properties should follow logically once the dependencies are established. This is an informal system but has proved effective and could easily, it is felt, be further refined and extended to a formal definition if necessary.

Temporal Logic

Science, especially physics, has long recognised time as a basic parameter. The problem of representing time is one of the major considerations of intelligent systems. Temporal reasoning systems have been produced which relate either to points in time (Soper et al 1991) or to intervals (Allen 1983).

At the simplest level, time is divided into three fundamental areas: past, present and future. Links between these areas are provided by words such as before and after. Temporal structures are either linear or branching. Linear structures are defined for all time, and time is reversible. Branching temporal reasoning assumes an open future; the future is unknown and several possibilities exist.

With classical temporal logic, it is impossible to say anything about the present time alone without saying "it has always been", or "it will always be"; this is clearly too limiting and has led to extensions to temporal logic by many people (Van Beek 1991, Console and Torasso 1991, Cousins and Kahn 1991). Van Beek, in particular, has taken Allen's original logic and extended it to incorporate the representation of indefinite time intervals. The theory is unfortunately too complex for use in current practical systems, so a simplified interval algebra

(SIA) has been defined by Van Beek which has solutions which are NP-complete and therefore practical for use in temporal reasoning systems.

The simplest way to represent the present is to use a clock and set the time of events recorded by the system to the current time; the concept of "now" can also be set by the user, either as a constant or changeable entity. Temporal relationships between events may then be built up by calculation of the time difference between the events. An option for representing periods through a typical day which has been used extensively in this research is to use meals as reference points and define the periods between meals using natural language phrases. For example, the period between *lunch* and *dinner* is *afternoon*.

Reasoning about Knowledge

An algorithm is defined as a process or rules for calculation. Algorithms usually presuppose that all possible outcomes are known and are usually categorical in the choice of outcome given the input. More recently, the concept of algorithms has changed to include explicit decision points where decisions are made with the data (or evidence) available at the time.

Heuristics are defined as advice (or rules of thumb) which are often effective, but are not guaranteed to be correct. An heuristic search is defined as a function that takes a state as an argument and returns a number, which is an estimate of the merit of that state, with respect to the goal. Algorithms and heuristics may be combined in decision making software; in particular heuristic searches often require algorithms for finding the best option and are therefore algorithmic at the lowest level.

Useful concepts which have been developed to explain reasoning include the goal-oriented problem space hypothesis. The original goal of AI was to give general problem solving search algorithms, which could be implemented to solve almost any problem. Since then it has been more advantageous to declare more specific domain knowledge, in order to solve problems in

expert systems, with a return to the separation of decision making rules from domain knowledge developed from application examples.

Searching methods are divided into breadth-first and depth-first searches. In depth-first searches a plausible line of solutions is followed as far as it will go, to the point where each solution is proved true or false. If one solution is false, then the next most plausible line is followed. In breadth-first searching the search proceeds along all possible paths building up probabilities of the most likely path to follow at each step.

The most common formalism for representing knowledge is as logical constructions known as production rules. They are of the form IF (premises) THEN (deductions). The premises of rules are termed antecedents, the deductions are termed consequents. The concept of rules was first introduced by Newell and Simon in the 1950s. In the early 1970s Buchanan and Shortliffe, among others, showed that production rules were appropriate and logical for the basis of knowledge-based systems (Davis et al 1977).

Two types of reasoning mechanisms are concerned with rule-based systems: forward chaining and backward chaining. In forward chaining rule systems a rule is fired as soon as its premises become true. Another method is to start from the goal and work backwards trying to find a logical path; this is known as backward chaining. Backward chaining is used when the goal is known, and we merely need to prove whether it is possible, or how it can be achieved.

Default Reasoning

If no information to the contrary is produced, then default reasoning may be used (Reiter 1978). Defaults are closely related to the use of frames, although the use of defaults is complicated by the notion of effects on the rest of the world. This is sometimes confusingly referred to as the frame problem (Hayes 1981); it is a difficult problem to describe in detail. Basically, it is impossible to describe all the properties of the world which are *not* affected by an event.

However, it is also likely that side effects of an event may occur. The frame problem is also related to the Gordian level of ignorance introduced in chapter 1.

An example of the frame problem is given by Dennet (1984): A robot is intelligent enough to know that it needs a new battery, the battery is on a trolley in a room in which there is a bomb. The robot correctly decides to pull the trolley out of the room in order to rescue the battery. But what happens if the bomb is also attached to the trolley? The robot can be made more aware in that it checks side effects of its action of removing the trolley. Now the robot considers every possible side effect - for instance that the removal of the trolley does not change the colour of the walls; this stifles it, so that it cannot come to a decision in time to save the battery and the bomb goes off.

In order to avoid these considerations, the "closed world" assumption is made in many intelligent systems. If an assumption cannot be proved then it is assumed to be false; this is also known as negation by failure in logic. For instance if the question of a patient's drugs arises, and a list of drugs has been entered, and aspirin cannot be found, it is assumed that the patient does not take aspirin. If no knowledge related to required information has been entered, for instance the question of whether a patient smokes or not is not explicitly recorded, then a question should be implemented automatically to discover the information. In the meantime the only knowledge which can be deduced is that the information is currently unknown but is of interest.

As rule-based systems are the most common paradigm for decision support systems/expert systems they are now covered in more detail. The clinic-based system developed in this work is a rule-based system; it is described in chapter five

Example of a Rule-Based System

Information items, or knowledge elements, are stored in a database which may also contain hard facts which are invariant. The combination of all these entities constitutes the basis of a

working rule-based system. Some examples of the major entities of a working rule-based system are given below: Questions are necessary to gain information from the user when a piece of information may not be gleaned elsewhere.

Question 1
Please enter blood pressure
diastolic .....
systolic .....

Rule 1
If systolic blood pressure > 100
then the patient is hypertensive

Fact 1
hypertensive drugs **include** "Captopril"

Question 2
What drugs are currently being taken?
The patient takes .....

Rule 2
If the patient **takes** Anydrug
and hypertensive drugs **include** Anydrug
then the patient **takes** anti-hypertensive therapy

Rule 3
If the patient is hypertensive
and the patient **does not take** anti-hypertensive drugs
then initiation of anti-hypertensive therapy **is** required

In order to decide if anti-hypertensive therapy is required, the system looks at rule 3, because it has the desired goal, it then tries to prove the first antecedent of this rule. This it does by referring back (backward chaining) to a previous rule which has this result, i.e. rule 1. This rule in turn tries to ascertain systolic blood pressure, there are no rules which have this result, so it asks the question of the user. The user may then supply an answer (or, if no value is available, enter the answer *unknown*). If the value entered is higher than 100, then the first antecedent has been proved, and that fact is added to the knowledge base. The system goes on to try the second antecedent, and backward chains to the question about current drugs. If "Captopril" is

entered as a current drug, then it will conclude that initiation of anti-hypertensive therapy is not required. However, if no anti-hypertensive drugs are entered, then the fact "initiation of anti-hypertensive therapy is required" will be proven, and further actions will be taken as necessary. One way in which this conclusion may be used is to fire rule 4, below.

Rule 4 **If** initiation of anti-hypertensive therapy **is** required **then** selection of best anti-hypertensive drug **is** required

This rule may, in turn, fire other rules, or it may initiate another backward chaining cycle, in order to find the best drug to be used. The above example demonstrates the main components of a knowledge base, and an example of the type of relational structure which may be built up. Words like "take" are defined as relations, so that they become key words. In this definition the opposite of takes has been defined to be "does not take"; if the expert system wants to prove A does not take B, it tries to prove A takes B, and, if it fails, asserts that A does not take B by the closed world assumption. This does not strictly follow from the rules of mathematical logic, but is a permitted extension within the decision making context.

Implementation

Once data structures are defined, and the implementation language has been selected or defined as required, a prototype system may be implemented. If the design stage has been thorough, this should be the simplest stage of the process. The selection of a development language will depend on hardware and software availability, as well as performance and safety considerations. Cullyer et al (1991), after studying and comparing several software languages, concluded that the safest language for the development of safety-critical applications is Pascal. However, languages such as Lisp and Prolog are more suited to AI program development. Many computerised tools are available for expert system design; these so called expert system shells enable the designer to quickly enter and test sets of rules. Often, a good strategy is to encode a specific problem, and test the logic, before moving on to large scale encoding of the background knowledge.

Further up the software-aided design scale come complete knowledge-base building systems. An example of a complete knowledge base design tool is KEATS (Motta et al 1988). KEATS includes facilities for knowledge acquisition, domain conceptualisation and interpreters to provide frame and rule-based solutions to a problem.

An expert system shell which does not restrict the method of knowledge acquisition, but includes powerful conceptual facilities for knowledge representation is the Xi+ system from Inference. This has been the development vehicle used for the clinic-based expert system described in chapter five.

Evaluation.

Requirements of decision support system validation are to evaluate: 1) The quality of the system's advice and decisions; 2) The correctness of the reasoning techniques used; 3) The quality of the human computer interaction; 4) System efficiency and cost effectiveness (Gaschnig et al 1983). Evaluation should be given a high priority and should be considered as an integral part of the build-test-refine cycle.

The evaluation of some classes of intelligent systems (notably rule-based systems) can be carried out by rigorous formal methods taken from mathematical logic. For example, Reiter (1988) has defined a knowledge base in terms of logic programming as a set of first order sentences. He has applied formal mathematical logic techniques to study the validity of knowledge bases by definition of integrity constraints. Integrity constraints are meant to characterise the acceptable states of a knowledge base and are used to enforce these states. They can be thought of as statements of what the knowledge base can be said to "know". Highly formal logic languages contain facilities to implement integrity constraints.

However, few systems correspond to the mathematical ideals of such models and practical evaluation of intelligent systems requires other simplified methods. A major problem with the evaluation of the results of decision support systems has always been the problem of how to

evaluate a system, when there are not necessarily any right and wrong answers, and there is considerable disagreement over the best strategy among experts. Ultimately, the evaluation of a medical computer system is in how it copes in the field in clinical field trials on real patients. Unfortunately, in early stages of development this method is ethically and legally unacceptable.

Another side of evaluation is physician and patient acceptance of the system. Does it encroach on the physician - patient relationship? A common method of evaluating computer advice systems is to run several test cases on the system and then ask experts to judge the systems advice with different criteria (table 2.4).

Table 2.4 Some criteria for judging system advice (answers could be on a scale of 1 to 5 say)
Is the advice:

- adequate?
- safe?
- useful?
- practical?
- adequately explained/justified?
- intuitively reasonable?
- returned quickly enough (performance question)

If the questionnaire is kept simple enough so that subjects may simply tick a box (perhaps on a sliding scale) this should not present too much difficulty in resources. The method of presenting the decision problems and outcomes to the judges should be as close to that found in normal practice as possible.

The major drawback of this system is it is not exhaustive of all possible scenarios; indeed as the system grows in size and complexity, it is difficult to ascertain how much it could actually deal with. The problems are highlighted even further if system designers are changed.

In practical knowledge-based systems, the syntax of the knowledge is structured and the relationships between different parts, (rules, static facts and so on) is well defined. In the case of production rule systems, the knowledge base may be systematically checked for the following problems:

Redundancy: Are any rules duplicating information or are they never going to be used?

Completeness: Are there any rules for which there is no way of obtaining the antecedents (either via questions or raw data)? This can be circumvented by the use of "automatic" questions for "missing" information.

Contradiction: Do rules produce conclusions which contradict with other rules in an illogical way?

Circular reasoning: A common problem with forward chaining logic is circular reasoning. A rule fires as many times as its antecedent is proven, and design needs to be careful, in order to prevent the presence of logical loops. A common way of doing this is to include a system for structuring the order of execution of the reasoning. Forward chaining may be limited to reporting outcomes "as they happen" and redirecting the system if an important fact is proven. The bulk of a system may then be encapsulated in simple backward chaining structures. It is normally much easier to follow logic (and provide simple explanation) from backward chaining than forward chaining.

The assessment of quality of human-computer interaction is largely a subjective quality, but some metrics may be defined. Usability criteria are outlined as (Clegg et al 1988): 1) ease of learning; 2) ease of understanding the core concepts, and 3) degree of consistency and lack of arbitrary commands. In addition, performance assessments should be carried out to check for delays in response times for complex queries and heavy processor usage. In general, users should feel in control and systems should not be unpredictable. The degree of effort, both physical and mental, required to learn and understand a system need evaluation, a minimum amount of key presses to undertake tasks is desirable and it is a general principle to restrict the depth of sub-levels in a selection system.

Performance aspects relate to system speed, the delays between requesting a service and receiving that service should be measured and assessed. Systems should notify users why any

delays are occurring when long delays are unavoidable, for example during a disk access procedure.

Ease of information input and output may be assessed by an error log. Error and error correction may be divided into "slips" and "mistakes" where slips are errors in execution while mistakes are errors of formation of intentions. The former shows an error of dexterity (either of mind or body), which possibly points to a physically difficult interface, whilst the latter is a more fundamental misunderstanding of what was required of the system and may indicate a change in prompt or screen layout is necessary.

Two measures of usability of an interface are Fitt's law (Thimbleby 1990) and Hick's law (Hick 1952). Fitt's law states that the time taken to move (the hand) to a choice depends logarithmically on the ratio of the target size to the distance which has to be moved to reach the target. Hick's law applies to selection from menus; it states that the user's decision time is proportional to the logarithm of the number of choices known to be open.

Fitt's law originally applied to movement of a cursor already placed on the screen, the distance moved (d) was the distance moved across the screen to the target of width w (equation E2.1).

$$T = a + b(\log(2d/w)) \qquad \text{(E2.1)}$$

Modifications need to be made to Fitt's law in order to cater for touch screens (Sears and Shneiderman 1991). Touch screens may not have a permanent cursor but the movement of the hand to the screen (in three dimensions) needs to be counted. For touch screens, Fitt's law takes account of the distance moved by the hand D, some measure of target size W and the distance moved to the actual target once the finger has been placed on the screen - this is assumed to be very small as the finger should be placed close to the target in the first instance.

$$T = a + b(\log(cD/W)) + d(\log(e/W)) \qquad \text{(E2.2)}$$

Knowledge base evaluation techniques include: Interviews, Questionnaires, System Walk-through, Formal observation (possibly video recorded), User diaries, System logging, Simple experiments (comparing two or more versions of the system or an aspect of the system; for example explanation types).

Experiments should be carefully formulated; stages in planning experiments are given in table 2.5 (Shneiderman 1987).

Table 2.5 Stages in planning experiments

1) Have a lucid and verifiable hypothesis.
2) Explicitly state what is being altered (independent variables).
3) Carefully choose what is being measured (dependent variables).
4) Judiciously select and assign subjects to groups.
5) Control for biasing factors.
6) Apply statistical methods and data analysis.

All the experiments outlined above suffer from the subjective nature of the assessment. There is a real need for some metric attached to the usability of an interface. One suggestion is the normalised performance ratio (NPR) (Moffat 1990). Equation E2.3 defines NPR as the mean of the periods of time required by a group of people to complete an identical processing task, divided by the sample standard deviation of those completion times. There is a correction for subjects who fail to complete a task altogether as this must be included as a failing of the man-machine interface.

$$NPR = \frac{\text{mean of the completion times}}{\text{sample sd of the completion times}} \times \frac{\text{successes}}{\text{successes+failures}} \qquad \text{(E2.3)}$$

Equation E2.4 defines NPR in terms of operational complexity (o.c.), processing task complexity (ptc) and solution complexity (sc). Moffat shows that the NPR is actually independent of these metrics as the mean completion time E(x) is proportional to these factors, although the argument used is mathematically flawed as factors which are cancelled are undefined.

$$NPR = \frac{E(x)}{sd(n-1)} = \frac{g(MMI\ oc, ptc) * sc}{\beta * g(MMI\ oc, ptc) * sc} = \frac{1}{\beta} \qquad \text{(E2.4)}$$

(β = sample coefficient of variation (cv).)

It can be shown (Moffat 1990) that β will remain approximately constant within all ranges of sc. This is one of the first attempts to produce such a metric, and is one which should be easy to apply to most user interfaces. Only time pressure prevented such assessments being carried out in the evaluations of the two systems described in the thesis.

Examples of Knowledge Base Validation - MYCIN, GLADYS and ANEMIA

MYCIN once again provides a classic example of a facet of decision support system development which has since become a large knowledge engineering task - the validation of intelligent systems. Validation of the MYCIN knowledge base was carried out in two stages: In phase one several human prescribers and MYCIN advised on test cases. In phase two, the human consultants assessed each piece of advice without knowing its origin. Classification of each piece of advice was into one of four categories: equal, acceptable, alternative and unacceptable. MYCIN compared very favourably with the human experts involved; it scored 70% acceptability to the majority of assessors. This result was, at first, thought to be disappointingly low, but the study produced the realisation of just how great the diversity of opinions is between experts. Indeed, it has been suggested that evaluation of experts takes place alongside evaluation of expert systems (Berry and Hart 1990).

A medical system which has undergone formal evaluation is GLADYS. GLADYS is the GLAsgow system for diagnosing DYSpepsia. In the experiment, doctors were trained to be familiar with GLADYS; then 202 patients were randomised so that the doctor received output from GLADYS for only one half of them. (Knill-Jones and Dunwoodie 1989).

A more complex example is the evaluation of ANEMIA, a system for management of anaemic patients. (Quagliani 1988). 30 cases where analysed, 5 by ANEMIA and 5 each by 5 experts. All the experts then saw the diagnoses and rated them as unacceptable, weakly acceptable, acceptable or ideal. This concentrates on evaluation of advice offered; other trials need to be done to assess usability, efficiency and cost effectiveness.

In any comparison experiment one should always watch for the Hawthorne effect (Roethlisburger & Dickson 1939), basically that improvement of performance in an experiment may be due to the monitoring and extra interest alone, and not due to the variable under scrutiny.

In some medical applications, simulation models may be built, which may provide input to the decision support system. Where decision systems use conventional algorithmic programming care should be take that the same assumptions are not explicitly included in the simulation model. In ideal circumstances, independent agents should produce a simulation model, perhaps employing different basic physiological models to that of the system designer, so that the validation can be as near as possible to a test of the model on real clinical cases. The use of simulation is thus limited to areas where a high level of physiological knowledge is available and may be modelled (for instance) using differential equations.

Lastly, the ultimate test of a decision support system is how it copes in the clinical setting. Properly controlled, randomised trials provide the best method of comparing computer assisted decision making with decisions made without the aid of a computer. Trials cannot usually be made blind, due to the nature of advice. Patients must know when they are receiving expert system advice and when they are receiving just default advice every day.

A possible option for use in a randomised trial may be to receive advice by telephone, half the time from an expert physician, and half the time from the expert system. Note that patients involved in this type of experiment are the ultimate decision makers and should accept

responsibility for their final decision. They could perhaps rate the value of the decision support given to them, or, less subjectively, the number of times patients followed the suggestions in each phase (the compliance) could be used to assess acceptability of suggestions.

Decision Support System Maintenance

Due to the evolutionary nature of medicine and the possible treatments, diagnostic tests etc. intelligent systems have a requirement to evolve and keep up with new developments. There is also a need for interactive knowledge acquisition when the system encounters previously unrecognised cases. Two solutions are possible: either full time knowledge engineers (or systems programmers to be more general) update the system in stages, or the system updates its own knowledge base (i.e. it learns).

Knowledge base maintenance is complicated, and several problems and proposed solutions have arisen. Addition of new rules or facts may have side effects. Occasionally a rule may be generalised or, in contrast, made more specific. An analysis of maintenance problems of the GARVAN ES1 system (Compton and Jansen 1990) suggests that experts do not report how they reach a decision, rather they justify why a decision is correct. These justifications are taken in context, and this must be taken into consideration in expert system building. Two suggestions are made for facilitating context changes in expert system development: ripple down rule bases and a knowledge dictionary.

The knowledge dictionary is an extension of the common data dictionary; rules are broken into their component parts and stored in a relational table, relational calculus can thus be used to manipulate the knowledge base in a much more powerful way than text editing.

Ripple-down rules are essentially ordered rule additions; when a decision or outcome is unsatisfactory to the domain expert, a new rule may be added after the last rule to be tried. All additions of this kind to the GARVAN ES1 are countersigned by a domain expert so the classification is easily done.

To assume that there are underlying primitive elements of knowledge structure derives from the "physical symbol hypothesis" of Newell and Simon (1972). The extraction of this deep knowledge is the most difficult task of knowledge engineering. Experts give justifications which appear simple as they are in context with the presented problems. This leads to simple addition of rules which is in contrast to general rules which are often opaque and difficult to maintain.

An intelligent entity has the facility to learn from experience. Human learning is viewed as a gradual process of concept formation (Gennari et al 1990), a succession of objects is observed and a hierarchy of events is induced to summarise these experiences.

The major successful paradigms for machine learning include inductive approaches, explanation based learning, genetic algorithms and connectionist learning methods. Early research in this area includes Feigenbaum's EPAM which concerned human verbal memorisation tasks (Gennari et al 1990). EPAM represents each instance of attribute-value pairs, along with an ordered list of component objects. Knowledge is organised in a discrimination network, where each non-terminal node specifies a test for deciding which link to follow from that node; one node is labelled OTHER to save all values having to be stated.

Lebowitz's Unimem (Gennari et al 1990) succeeded EPAM and introduced some novel ideas; natural language understanding and inference were the goals. In Unimem both terminal and non-terminal nodes have concept descriptions which may be numeric and may have associated weights.

Fisher's COBWEB (Gennari et al 1990) uses the theory that some concepts are more "basic" than others. It links parents to children by "is-a" links in the hierarchy. Four processes take place: (1) classification of objects into existing classes, (2) creation of a new class, (3) combination of two classes into a single class, (4) division of a class into several classes.

CLASSIT (Gennari et al 1990) is a new model which embodies much of the earlier systems and attempts to improve upon it. CLASSIT models concept formation with real valued inputs, this leads to evaluation equations concerned with statistical distribution combinations. It is particularly strong on evaluation of missing attributes by a statistical method employing the standard deviation.

Explanation based learning (EBL) (Minton et al 1990) improves problem solving performance through experience. Explanations are converted into operational recognition rules. The method is thus knowledge intensive and analytical. STRIPS (Fikes & Nilsson 1971) is perhaps the most influential precursor of EBL; it solves a given problem and then converts its set of macro-operators to solving similar problems in future. PRODIGY is described by Minton as an example of an EBL system.

Derivational analogy solves a problem by replay of a plan used to solve a previous problem, modifying it where necessary. POPART (Mostow 1990) generates a suite of grammar related tools intended to support the transformational development of specifications and programs. It has facilities for recording, editing and replaying a sequence of steps.

Connectionist learning methods are popular in areas where pattern recognition is involved. Ambitious projects designed to imitate actual brain processes led to the name neural networks for this type of learning system (Pao 1990). Neural networks consist of massive numbers of processing elements, called units, which interact through weighted connections. Long term knowledge is encoded by the locations and weights of the connections and processing is concerned with adding or removing connections or changing weights. Connectionist learning methods are a popular current area of research but suffer from a lack of ability to justify or explain their reasoning and difficulties of system validation. It is also difficult to represent higher level conceptual knowledge in connectionist networks so they are often employed as part of an intelligent system along with a frame or rule based formalism.

The neural network approach has been utilised in the AEDMI program (Ferrer-Salvans and Alonso-Valles 1990) in order to filter subjective diagnostic probabilities supplied by a large number of physicians on various cases. In this way it is hoped to create a large central database for decision support.

EXISTING MEDICAL DECISION SUPPORT SYSTEMS

Early decision support systems which reached research prototype level include ONCOCIN (Shortliffe et al 1981) - a rule-based expert system for managing cancer patients and GUIDON (Clancey 1979) which instructs students in the selection of antimicrobial therapy for hospital patients with bacterial infections and also utilises the rule base of MYCIN. Originally, MYCIN was concerned with antimicrobial therapy selection; it was developed at Stanford University during the 1970s and has become the most well-known and oft-quoted AI program of the generation. Starting as a simple rule-based expert system written in the computer language Lisp, it evolved into EMYCIN and NEOMYCIN which provided structural languages for knowledge engineering, a meta level of reasoning above the domain specific knowledge of MYCIN. A language translator provided explanation capabilities on two levels, a simple *why?* capability which translated rules and an interactive question and answer capability.

Frames were utilised in systems such as PUFF and WHEEZE (Aikins et al 1983) which were aimed at pulmonary diseases. An amalgamation of frame-based representation techniques with rules still provides one of the most fruitful systems for constructing expert systems. For more detailed information about medical knowledge based systems see Fieschi (1990), Giarratano and Riley (1990), or the classic reference book by Waterman (1986).

General Medical Systems

General practitioners are, as the name suggests, non-specialists. For this reason they undoubtedly experience more uncertainty when faced with unusual problems in newly

presenting patients. The acquisition, classification and judgement of symptoms, clinical tests and previous history is a complex process. For this reason computer decision support and database systems are gaining in popularity for GPs and two proposed systems are described below.

GPs' responsibility for patients with chronic, ongoing diseases is on the increase. GPs now often run mini-clinics concerned with such problems as hypertension, asthma and (probably most common among chronic conditions) diabetes. Decision support for these medical conditions is vital if optimal care is to be provided for all patients.

The interactive nature of health care has led to the proposal of a massive knowledge base to cover the whole field of medicine (Fox et al 1987). This ambitious project, the Oxford System of Medicine, has been developed since 1986 by clinical and computer science researchers at the Imperial Cancer Research Fund in London with funding partly by Oxford University Press and the European Community AIM project LEMMA. The project is progressing well (Gordon et al 1990) and is now in a second phase of three years, within the DILEMMA project. Presently, the OSM database contains knowledge on diagnoses within several chosen medical fields and is particularly complete in the areas of joint pain and breathlessness. Extensions to the functionality have enabled the model to support the use of clinical guidelines, in particular a guideline for the management of hyperlipidaemia has been implemented and a diabetes guideline is planned for 1993. The current system implementation is based on an IBM compatible PC with software written in Prolog and C. Its user interface incorporates WIMPS facilities and intelligent data input aids such as string completion. A new version, written entirely in the C language should overcome restrictions due to PC memory and speed of processors and will enhance cross-platform portability of the system.

The OSM is interesting mainly due to its implementation of a separate set of procedures for decision making. Decision making in the OSM consists of five stages, (1) candidates are proposed, (2) they are endorsed with arguments that support or refute the candidate (the

candidate could be related to a diagnosis, investigation or treatment problem) (3) the candidate can be evaluated, either qualitatively or quantitatively. (4) relationships with other candidates are examined to see if any could coexist or are mutually exclusive and (5) a candidate (or candidates) may be selected to form a decision. Automatic truth maintenance is included to provide logical consistency of assertions made.

Acceptability of the system may be enhanced by its flexibility. An interactive evaluation facility provides the opportunity for physicians to suggest their own decisions for the system to discuss, as well as allowing the physician to view all the possible, supported, eliminated and confirmed candidates in a situation.

Integrated with the OSM is an interface to the CD ROM edition of the Oxford Textbook of Medicine, a major reference textbook. Another useful feature built into early prototypes is a browsing facility to allow examination of this and in particular the medical information on which decisions are based. This style of presentation is called hypertext, the use of such methods is known to be highly attractive to medical practitioners (Timpka 1990). The internal random coding system presently used for the Oxford System of Medicine is expected to be linked with the Read codes as they become a standard in the medical informatics field in this country. However, many deficiencies are present in the Read codes and the long term goal is to link with the research of other AIM projects to provide definitive solutions to the various areas of clinical computing which are presently perceived as a problem.

A similar browsing system with potential for decision support has also been developed by a team of medical informaticists from Manchester University department of Computer Science, led by Rector (1991). The current implementation of the system is in Smalltalk on an Apple Macintosh or Sun workstation and now includes hierarchical data structures and an extremely sophisticated user interface combining text and graphics to simplify entry of data on several levels. The Pen and Pad system is eventually to be aimed at the GP level and is set for beta testing in June 1992. The fully developed user interface would subsequently be linked to

modules to provide decision support on therapeutic and diagnostic decisions and the type of drugs to administer. This could well be the Oxford System of Medicine or a system developed from it.

The two general systems outlined above provide sophisticated frameworks for medical expert systems but the substance of decision support still remains to be added. Massive expansion of the OSM database from its present 15,000 to an estimated 10 million facts is now feasible within the PC environment (Gordon et al 1990) given data storage requirements of individual facts within the system. An advantage of the Manchester system is its syntactic knowledge representation schema. Levels of abstraction are available to link concepts of disease to individual entities and to different parts of the body through textual and graphical interfaces. This work is also continuing within the AIM programme in the GALEN project, which aims to produce a generalised architecture for terminology used in medical systems.

Patient-Oriented Medical Systems

The vast majority of systems so far designed have been aimed at the non expert physician or General Practitioner level with only a few recent examples of systems offering advice directly to patients; many of these are within the field of diabetes (Albisser et al, Schultz et al, Schrezenmeir et al 1985b). In the next chapter, existing computer systems in diabetes care are described and their impact on the decision making capabilities of physicians and patients who use them.

CHAPTER 3 - COMPUTER SYSTEMS IN DIABETES CARE

COMPUTER RECORD KEEPING

Diabetes has often been used as the paradigm for medical uses of information technology and intelligent systems. Most large hospital diabetic clinics and some GPs who run diabetes clinics now have computer databases to store patient details, results of biochemical analyses and so on. One possible reason why diabetes is often selected as a medical domain by informatics researchers is the multiplicity of links to other specialities which all too often occur in diabetes. The motivation appears to be that links to cardiovascular problems, eye problems, neuropathy, nephropathy and chiropody (the most common complications of diabetes) will enhance the comprehensiveness of the computer system under development. It is not uncommon for a patient to be seen by three or four specialists, as well as a dietician, all of which would benefit from a detailed description of the patient's diabetes.

Patient databases typically contain basic background data such as name, hospital identification number, age, height etc. This is then updated with details of specific information such as results of biochemical analyses and may be useful for the production of ideal weights for patients and for checks on routine tests which should be regularly carried out to monitor eyes, kidney function, nerve responses and blood pressure. Analysis of patient databases can help with policy decisions. The possibility for on-line data entry and recollection now exists but is limited by availability of resources and by the existence of physician reluctance as outlined in chapter two.

DIABETA is an example of a system which has been accepted into clinical practice. It has been in use in St Thomas' hospital for 8 years collecting data interactively in the diabetic outpatient clinic. The system has included the development of a limited "intelligent" advice system to provide therapeutic advice, general advice, advice on screening and investigations, referrals, timing of next visit and content of the next visit. The system is written in Prolog and contains

over 1000 rules whose logic has been validated. The system has been evaluated both in the laboratory and by experienced diabetologists.

DIABETA currently holds records of 5600 patients. An example of the benefit of computerisation occurred when the system was used to indicate risk factors for diabetic nephropathy (Tsuruoka et al 1991). Proteinuria positive patients were examined (that is patients whose urine sample contained a detectable level of protein). Risk factors did not involve smoking, alcohol consumption, duration of diabetes, sex or obesity. There was significantly worse glycaemic control in these patients. Patients also tended to be older at diagnosis, and the group contained a higher proportion of affro-carribeans than the population as a whole. More strokes were present in the maternal cause of death and there was a higher incidence of raised blood pressure. The report, compiled with the aid of DIABETA, adds more evidence to indicate the importance of glycaemic control, and of a personal and family history of hypertension in the development of diabetic nephropathy.

Such retrospective analysis of patient databases is enlightening but the properly controlled, randomised studies of the UKPDS should provide more concrete evidence of the connection between management strategies and incidence of complications when the final reports are published some time in 1993-94.

GLUCOSE MONITORING

As outlined previously in chapter one, diabetic management now centres on home blood glucose monitoring (HBGM), which is also referred to as Self Monitoring of Blood Glucose (SMBG). Urine measurements are limited to providing an indication of hyperglycaemia, they depend on the net result of two processes: glomerular filtration and tubular reabsorption; differences exist among individuals in these mechanisms and this produces differences in glycosuria for given blood glucose levels. Urine monitoring is therefore only recommended in

cases where patients are unable to carry out SMBG or in elderly type II patients with very stable diabetes and no complications or symptoms treated with minimal therapy.

Two major methods exist for the measurement of blood glucose. The first method involves a chemical reaction between the glucose content of the blood and chemicals in a strip which changes the colour of the strip. The level of blood glucose may then be read off against a colour chart by eye or special meters may be used to assess the level by photogrammetric reflectance techniques. A second method involves electrical resistance of electrodes, no colour change is involved, instead a drop of blood is placed on the electrode and a direct amperometric reading is attained.

The advantages of the first system are that a visual check may be made by patients as well as the use of the meter. Many of the meters also contain memories for storage of several dated and timed glucose measurements. Disadvantages of the system are the time delay between taking the sample and obtaining a response, this may be two minutes or more and can be inconvenient if patients need to measure glucose at work for example.

The advantages of the second system for decision making are its speed (30 seconds) and accuracy. In tests, the amperometric meter produced results which were more closely correlated with results of laboratory methods of measurement than the reflectance meters. Amperometric meters tend to be much smaller and are therefore more likely to be carried and used regularly by patients. Disadvantages at present include the lack of a memory (patients still have to enter the measurements by hand into a log book); there is also no way of validating the meter's readings apart from a second opinion gained when patients attend their clinic as the strip does not change colour. In time these problems will probably be overcome and the reliability and availability of meters should continue to improve in order to provide this essential prerequisite for optimal blood glucose control.

REPRESENTING AND INTERPRETING GLUCOSE RESULTS.

The link between glycosylation of proteins and the incidence of diabetic complications suggests that the most important pointers to adequacy of glucose control are the mean blood glucose and the variability. It has been shown (Holman and Turner 1980) that in type II diabetes meal time insulin responses are often sufficient to overcome the associated rise in glucose due to the carbohydrate content of the meal. The meal time rises in blood glucose, or post-prandial glucose excursions as they are called, are superimposed on a raised fasting blood glucose level. Monitoring of type II diabetics may therefore be carried out by measurement of the fasting glucose only and decisions as to the appropriate therapy may be made based solely on the fasting blood glucose until the B cell function is impaired to the level where meal time insulin is required.

Type I diabetes requires more frequent monitoring as little or no functional B cells remain and insulin has to be supplied to cover meal time excursions.

Mean blood glucose, represents glycaemia in a simple way but gives no indication of variability and depends on timing and frequency of measurements. If limited to fasting and/or preprandial measurements it may be more representative. More intensive monitoring regimes suggest a sampling scheme of preprandial and post prandial (90 mins after meals) measurements. Reasonably good correlation was observed between this 7-point system and an even more intensive 22-point measurement regimen (Service et al 1987).

Measurements of extremes of glucose have been proposed as alternative indices of glucose control. Variability may be quantified by a peak to nadir ratio, or a standard deviation, or a ratio of some other arbitrarily selected points to represent high and low portions of the scale of measurements. However, there is still no indication of the distribution of the measurements through the day.

Other indices of control include mean amplitude of glycaemic excursions (MAGE), which is a measure to quantify major swings post meals (80 mins), and includes values greater than 1 SD. The mean indices of meal excursions (MIME) describe post prandial excursions as time from the start of the meal to the peak of glucose and are suited to continuous glucose monitoring systems only. For non-diabetics MIME parameters are typically 45 mins +- 5 mins.

Problems with measurement exclusively of the fasting blood glucose came to light with the discovery of the dawn phenomenon. It is thought that glucose levels start to rise in both normal and diabetic individuals at around 4-5 am in readiness for waking up. The study of Schmidt et al (1981) placed the dawn phenomenon within a new conceptual framework with regard to its relationship to intra day blood glucose variation. The dawn effect was positively and significantly correlated with measures of variation including CV and MAGE. Also its consistency in the patients, despite variations in daily living parameters, suggests it may be a universal factor in all type I diabetics.

Decisions concerning night-time insulin therapy are a particularly contentious area. Many studies have been carried out to compare various insulin formulations (Riddle 1990). Night-time or evening insulin strategies are dependent to a great extent on empirical findings. Riddle advocates a trial and error approach to finding the most appropriate regimen for individual patients. The basic variables are duration of action of the insulin, the time to peak, timing of delivery, whether to include some short acting insulin (either a separate formulation or a mixed insulin type) if the dose is given with the evening meal. In extreme cases sulphonylurea may be given in conjunction with insulin, although the success of this approach depends on the amount of residual beta cell function.

Studies have been carried out to compare continuous subcutaneous insulin infusion (CSII) with multiple subcutaneous injections (MSI) and have found no significant difference between glucose control due to the two methods. Haakens et al (1989) investigated the effect of different therapy regimens on the fasting glucose. He concluded that CSII was better than MSI

for controlling morning glucose. Human isophane injected before bed produced lower glucose than ultralente. However, when the breakfast meal was delayed glucose rose in CSII and isophane use, but remained stable in ultralente use. Attempts were made to increase the ultralente in order to reduce fasting glucose but patients reported afternoon hypoglycaemia. This may be because of a shorter half-life in the ultralente which theoretically has no discernible peak level. A better distributed diet may also have alleviated the hypo problem while allowing reduced fasting glucose, as exhibited by many existing users of the basal prandial insulin regimen (chapter four). As already stated, patients do not generally want the inconvenience of a pump to constantly remind them of their diabetes so MSI is considerably the best current option for optimal control.

Some reports suggest that human intermediate acting insulins are absorbed more quickly than animal species, adding to the complexity of matching an insulin to the requirements of the individual. Other factors concern administration, i.e. site, temperature, physical activity and inherent absorption characteristics and all should be taken into consideration.

In order to quantify the dawn phenomenon investigators coined the term FAGE for fasting ascending glucose excursion, this is the difference between pre-breakfast glucose and the nadir occurring overnight. Schmidt also noted that the FAGE was greater than both the midday meal MAGE and the evening meal MAGE, despite the patient eating identical meals.

The M-Value

An innovative parameter developed in the 60s (Schlichtkrull et al 1965) is the M-value. This formula (E2.5) provides a single numerical quantity for describing control in terms of mean and swings by means of a logarithmic transformation of values compared to the standard reference value.

$$M = \text{sum}(\text{abs}(10 * \log (BG/120)^3)) / N + W/20 \qquad \text{(E2.5)}$$

where BG are the N blood glucose determinations, W is the total range, i.e. the difference of the highest value minus the lowest value. The reference value of 120 may be changed to suit individuals (measurements should be in mg/dl). The advantage of this system is that it gives a measure of normality of control, high blood glucose values increase the figure, but very low blood glucoses record still higher M-values. It is recommended (Service et al 1987) that a profile of 8 blood glucose readings, four pre-prandial and four post-prandial readings, should provide an optimised indication of overall control. In practice, the four preprandial blood glucoses are usually recorded and in the clinic POIRO management system the M-value for preprandial blood glucoses is plotted beside a graph of the moving average blood glucose before each meal. The differences between a seemingly good (i.e. low) blood glucose and the M-value can be quite great. This may indicate asymptomatic hypoglycaemia which is undetected, or may indicate that lower levels of blood glucose are obtainable and the reference level of the M-Value should be tailored to individuals. However, the latter option makes it impossible to standardise control parameters between individuals.

Long Term Control

Long term control may be defined as an overall value which describes blood glucose values over an extended period of time. It may be measured by glycaemia directly as above, or by some other assay independent of blood glucose measurements. A common assay at the current time is the measurement of glycosylated haemoglobin (HbA1c) (see chapter one) which gives a measure of control over the previous 2 to 3 months.

Fructosamine, the condensation product of glucose and proteins formed by the reduction of the osazone of glucosamine, has also been observed to relate to glycaemia, with positive correlations to fasting glucose and HbA1c levels. The duration of fructosamine is about 3-6 weeks.

Emphasis on hypoglycaemia is recommended as continuous monitoring has shown quite high prevalence of asymptomatic hypoglycaemia, especially in intensive insulin therapy. The M-value, as described above, places special emphasis on hypoglycaemia, which may be varied by variation of the reference value. It may therefore be a most appropriate single measure of adequacy of overall control but may be too complicated an entity to be used in clinical decision making.

Most of the systems currently under development for physician decision support concentrate on interpretation and representation of home blood glucose measurements (Rodbard 1988, Cohen 1991). Glucose meters with built in memories may be directly connected to the physician's desk-top computer and the data transferred and examined in various statistical and graphical overviews. Alternatively, log book recordings may be transcribed to a computer for analysis, although this is a tedious and error-prone method. Log book reports of blood glucose have been shown to be error prone. Mazze et al (1985) conducted a study in which patients used a glucose meter with a memory and recorded the measurements in their log books: the patients did not know of the memory. The results showed that patients often fabricated "good" (normal range) glucose results and did not report "bad" (high) glucose test results. In a later study, patients were made aware of the memory and almost 100% accuracy of recordings followed.

Wilson and Clarke (1983) made an early attempt to present raw HBGM data. Results taken from patients' log books were transcribed to a computer as one dimensional arrays. The x-values were the time variable and y-values the readings. The x-values were further coded by date and time of day; the date was set as an integer starting from day 1, decimal extensions were applied to give the time of day as follows: 0.20 = 3 am, 0.40 = pre-breakfast, 0.42 = post-breakfast etc. This method has the advantage of retaining the one dimensional nature of the array but loses the actual times of glucose determinations. The program code was written in BASIC, with graphic routines in a Hewlett-Packard graphic language. Raw data or the MAGE (mean amplitude of glycaemic excursions, described in Service et al (1987) index of glycaemic

excursions may be plotted. Three interpretations of the MAGE were used: The average absolute amplitude of values compared to the daily mean, average absolute amplitude compared to the grand mean of all the data, the mean of daily absolute differences from the mean glucose minus one standard deviation (mean and SD of whole data set). The resultant graphs were still difficult to interpret and more conclusive interpretation methods have since been developed.

The Ambulatory Glucose Profile

The phrase 'Ambulatory Glucose Profile' (AGP) has been coined (Mazze et al 1987) to describe one method of assessment of home monitoring on a computer screen. The profile is a plot of a period (usually two weeks) of glucose determinations; usually the median and quartiles are plotted for each hour throughout the day although sometimes other percentiles may be plotted provided there are enough readings.

The plot gives a representation of glycaemic control over the period studied and highlights grossly bad control. However, due to its hourly nature, it does rely on regularity of meals and insulin injections.

A meter with a memory is virtually essential for accurate presentation of blood glucose test results. Some method of transferring the data to a larger physician oriented personal computer is also essential for physician analysis within the limited time-scale of a clinic consultation. In cases of limited memory within the glucose meter, data transfer by modem has been put forward as a possibility (Zimmet et al 1988), although the method could prove expensive if frequent data transfer is required.

ELECTRONIC LOG BOOKS.

Some systems have gone further than merely analysing glucose determinations and produced a computerised patient log book for recording dietary carbohydrate, insulin doses and exercise as

well as glucose values (Rodbard 1988). Systems for use by patients divide into those based on commercial programmable calculators or pocket computers and custom built devices.

The CAMIT system (or MERLIN as it is called in the USA) is an example of an electronic diabetes log book based on a programmable calculator. The system has been modified since it was originally designed as a therapy adjustment program and has gradually evolved into a monitoring and interpretation system. The original system (see below) was integrated with the Reflolux blood glucose testing system (manufactured as Accu-chek in the USA and Canada). The software was divided into three components. A custom built device, known as the CAMIT EL (Electronic Log) is connected directly to the reflolux reflectance meter. It stores data on other events and insulin doses as entered on a combined pictorial and numerical key pad. Data is transferred to the serial port of the physician's Personal Computer via a link module CAMIT IF. The PC runs the software CAMIT S which does the evaluation and simple graphical displays of the collected data. The insulin dose adjustment function of CAMIT is described later in this chapter under the heading of computer advice systems.

A custom built system - DIACRONO (Gomez-Aguilera et al 1987) - includes facilities to enter diet in terms of calories and nutrition, exercise from a subjective evaluation of three discrete levels, glucose measured in the patient's normal way and insulin dose. A four option menu-driven system is employed for choice of data entry. Numbers are entered on an in-line ten key pad. The interesting aspect of the system is that it prompts for input at set times, known as assessment intervals (AIs). The system also has facilities to allow it to be connected to a desk-top computer work station which is used to adjust insulin doses and diet with or without the aid of a physician.

The DIVA system (personal communication) consists of a custom built hand held electronic log book. The patient device (named Romeo) connects to the physician's computer (Homer) via a connection unit (Juliet). The Homer system provides for display and interpretation of the data collected by Romeo. There is no advisory capacity within the system however, so it is limited

in use to experts who merely require more information than can be gleaned from an ordinary log book.

Diabetes Education.

Many patients have suggested a more education-centred approach to diabetes care (Coles 1990, Parrot 1990). Criticisms of traditional consultations include the limitation to basic medical factors, such as current doses, frequency of monitoring etc. whilst more detailed explanation and information about what may be done with glucose test results is overlooked. Coles suggests that there should be more encouragement of patients to ask questions and lead the consultation.

Considered as the first priority by many is education of how to cope with newly diagnosed diabetes as well as continued education throughout the duration of the disease. It was thought that well motivated, knowledgeable patients would be more likely to carry out regular glucose monitoring and to adjust insulin doses (Mazze ibid.).

Bloomgarden et al (1987) suggested that patient education may not be an efficacious therapeutic intervention in most adults with IDDM. In studying 345 patients, 165 were given intensive education whilst 180 controls received normal therapeutic monitoring and advice. HbA1c fell in both groups with a slightly greater (but non significant) fall in the education group. Similar results occurred with the fasting glucose.

No differences in qualitative variables such as hospitalisations, sick days off work etc. were reported between the two groups. Guidelines for patient education have been released (Alogna 1983) and in the Bloomgarden study 54 criteria relating to knowledge and behaviour were included in questionnaires administered to each patient. The education program consisted of monthly education sessions, with each session concentrating on a single aspect of management of diabetes. The patients were subsequently divided into graduates (those attending at least 7 of the 8 sessions) and non-graduates (< 7 sessions attended).

There were no significant improvements in knowledge and behaviour between education and control groups in total, but a highly significant difference between graduates and the control. HbA1c was not significantly different in any of the education or control patients whether graduates or not.

The education program contents may have been a factor in the negative result of the study; the program did not employ increased HBGM, self-adjustment of insulin doses or increased clinic visits but concentrated on various aspects of the illness and in particular on nutritional recommendations. Special education programs may be meaningless unless they correspond with improved control and less likelihood of complications indicative of better health. This study indicates that even patients with high knowledge of the disease are still not sure about alteration of therapy, decision support could help them over that hurdle.

More success has been claimed with computer aided education systems. Dammaco (1989) showed that knowledge levels of adolescents were higher when computers were used for instruction than cases where instruction was provided by booklet or group sessions.

The Eurodiabeta Initiative

The Eurodiabeta project was a European Community supported project within the Advanced Informatics in Medicine (AIM) exploratory phase. The project was proposed to examine the feasibility of applying information technology to improve health care in the field of chronic disease using diabetes as an example. In April 1990 physicians and information scientists from all over Europe met to examine the potential of the project in a series of workshops. The Eurodiabeta consortium consists of a balance of clinicians, informaticians, computer scientists and industrial partners set up to ensure systems designed and built fit in with current medical practice. Table 3.1 displays the six declared aims of the project.

Table 3.1 Aims of the Eurodiabeta project
a) Development of a conceptual model of diabetes health care delivery
b) Consensus on a diabetes data set for medical records in different health care settings.
c) Development of evaluation methods for knowledge based systems.
d) Development and assessment of model and knowledge based methods for assisting in insulin dose adjustment.
e) Computer assistance in diet management.
f) Identification of non-technical barriers to the introduction of information technology based systems.

Workshop 1 dealt with modelling aspects and concluded that the method is appropriate and applicable to diabetes care and also considered it likely that the method of defining medical structure and decisions by a developmental modelling tool could be adequate for a complete description of diabetes care.

The technical aspects of modelling were addressed in workshop 2. Software packages were used directly by clinicians to build up and validate conceptual models of medical practice. This "prototyping" methodology enabled clinicians to interact directly with "the machine" in order to produce models for input to system designers. The ability to model decision processes and the provision of advice on how to manage a specific problem were considered the most useful features of the system.

Workshop 3 considered the introduction of a diabetes data set. A hierarchy of data sets were proposed, including a Top Level Monitor consisting of a condensed extract of the data set. This design established a problem oriented report characterising a patient's actual metabolic and health status with special emphasis on secondary complications, risk factors and current therapy.

Workshop 4 evaluated the diabetes data set defined in Workshop 3 with reference to a set of test cases taken from clinical practice. The need for further data items inevitably arose, highlighting the deficiency of the initial definition. Further review of cases with incrementally updated data sets produced a data set which was considered complete for a description of the clinical status. However, a major criticism of the data was that medicine is necessarily a very

holistic process and data items on human factors are also necessary and would be useful for assessment of general well-being and psychological adjustment. The impact of diabetes on the whole patient would then not be misjudged by merely examining hard facts.

The problem of "soft" data needs to be addressed with considerable care. In some cases the information is gleaned directly from the patient; e.g. on hypoglycaemia. In other cases, the patient may be on medication for a psychological problem or the doctor may have personal knowledge of patients and may use knowledge of their very individual social and psychological conditions in management decisions. It is this type of doctor/patient assessment which is difficult, if not impossible, to encapsulate in a knowledge-based system.

An example of incorporating patient preference is implemented in the POIRO patient-oriented system to be described in the next chapter. This concerns the risk of hypoglycaemia and is described as follows. Given a one in a hundred chance of a hypo if an insulin dose is increased, some patients may opt to remain at high glucose levels, despite the greater chance (one in three perhaps) of eventually getting microvascular complications such as nephropathy which can lead to renal failure and early death. Of course, the decisions are not as clear cut as this, and the effect of high glucose on proliferation of complications has not yet been completely established. Patients are made aware of these risks however, and the decision of whether to adjust therapy is often reflected back on them in asymptomatic cases.

Computer Advice Systems

One of the first attempts to offer advice was the SUGAR-1 system (Pernick and Rodbard 1986). It provided a mechanism for developing customised treatment plans and provided a retrospective analysis function. The program still expected the physician (or clinical assistant) to type in a month of information and so was rather unfeasible for wide scale use. The program advised changes both in individual doses and in the insulin regimen.

Dose adjustment combined with educational programs aimed both at teaching physicians and patients have been developed with various degrees of success. An interactive educational expert system for providing personal advice and therapeutic recommendations, SESAM DIABETE, (Levy et al 1988) became available on the French MINITEL network in 1988-89. This powerful system is written in a Lisp based shell (LISP.MBX) under VAX VMS. It allows the creation and use of semantic networks with multiple inheritance to provide explanations to users.

The medical knowledge within SESAM DIABETE is encoded into 560 frames used to describe medical entities and 300 principles relating to specific subjects such as hypoglycaemia. Then there are 30 causal relationships such as:

Decrease of Insulin ---- Induces ---> Increase of Glycaemia.

In order to use the system a goal is set such as check the patient's knowledge of hypoglycaemia. A search is then initiated which looks for relationships where the consequence is a decrease in Glycaemia. i.e. X ---- Induces ---> Decrease in Glycaemia. Other checks may also be advised such as whether the patient knows signs and symptoms of hypoglycaemia. The details of the system do not indicate whether it advises on day to day individual treatment alterations, although general problems such as what to do about exercise or travelling are dealt with in detail. A natural language processor is employed at the front end of the system making it reasonably friendly to the user. The system does seem to have a lot of promise but suffers from the drawback of its size, and the time taken to access it may discourage regular use. Results of clinical trials of the system are awaited with great interest.

Computerised advice or analysis systems for patients were limited in scope until the last few years as few patients own personal computers (and even fewer IBM compatibles) and the few programs that were available for patients provided alternatives for the day ahead and required the patient to type in timed events at the end of each day before prescribing for the following

day. SUGAR-1 had a patient oriented facility for data entry which was quite advanced in outlook but required an enormous amount of time and motivation from the patient. Patients with diabetes have repeatedly stated that they are not prepared to inconvenience themselves any further by having to spend extra time and energy on a computer system.

In the last five or six years the increasing miniaturisation of microcomputer devices has made sophisticated pocket or hand held computing power available at a reasonable cost. There have been several attempts to program a device to advise insulin doses to insulin dependent diabetics on a daily basis.

The Insulin Dosage Computer (IDC) is one such device (Albisser et al 1985). It is based on a pocket calculator with a specialised keyboard and a tiny LCD calculator style display. The system prompts for blood or urine glucose measurements to be entered four or more times per day at fixed times, it then advises insulin adjustments based on a modified version of algorithms published by Skyler et al (1981). The device has capabilities for adjusting doses to take account of exercise and a facility for entering hypoglycaemic reactions. The main drawbacks of the device are its inflexibility, user interface and speed.

The algorithms use a simulation to produce expected glucose levels and this often means a 30 - 40 second wait for a prescribed dose after entering all the other information. It has also suffered because of its limited memory capacity and lack of a full audit trail, especially its assumption that patients took the advised dose at all times. The device has recently been refused in the USA by the FDA until modifications are made.

The CAMIT system described earlier had a component which was a hand held insulin dose computer system. It was devised by researchers at the University of Mainz medical school (Schrezenmeir et al 1985b) based on the popular Sharp PC-1500. The adjustment algorithms used adaptation formulae based on data obtained by the artificial pancreas (Biostator). The algorithms developed for the CAMIT system are complex and require patients to enter gram carbohydrate equivalents for every meal. The adaptation formulae convert daily insulin need

on conventional therapy (DINCT) into appropriate basal prandial doses to be given by multiple subcutaneous injection (MSI) or via a pump.

Clinical trials of the CAMIT dose adjustment device in twelve patients produced extremely good results in terms of significant reductions in blood glucose (Schrezenmeir 1985b). However, the use of the device coincided with the change to intensive therapy from twice daily injections of mixed insulin and so the results are somewhat misleading. The device showed a reduction of insulin need on the different therapy and a concomitant reduction in the number of meals per day. No information on weight was included. The system of algorithms demands rigid timing over meals and insulin doses and assumes that the advised dose is rigidly followed; thus the device, while successful, could not be used by the uninitiated or less motivated individual.

The device is not user-friendly; it has a tiny conventional keyboard and small one line display and therefore is restricted in its use to those with computer skills or who are willing and able to learn those skills.

Most of the systems so far described have been limited in their decision support content and even more limited in the AI content. New systems are now appearing which do attempt to use AI techniques, either alone, or in conjunction with mathematical models and algorithms. One such model (Deutsch et al 1989) aims to develop a dynamic model to predict outcome and plan treatment whilst providing explanation/justification for the treatment. The system concentrates on insulin adjustment but is expected to be upgraded to include dietary and exercise advice in the future.

The management of diabetes is described in terms of a control problem: the pancreas' normal secretion breaks down so insulin therapy is required. Distinction is made between acute cases of bad control due to diabetic coma, and longer term control problems due to variations of glycaemic control over days to months. A simple diet prescription is included, which gives amounts of the main constituents to include in meals. Four insulin regimens are covered, R1 =

two intermediate injections, R2 = two mixed injections, R3 = 3 injections per day of short, intermediate or mixed insulin, R4 = 3 short acting injections to cover meals and 1 intermediate acting injection before bed. Ultralente insulin does not appear to be covered. The injection site is explicitly stated and may be varied between femoral and abdominal.

Eight characteristic times for blood glucose monitoring are defined, before and two hours after main meals and at bedtime and dawn (2-4 am). Target values are rigidly set at 3.5 to 7 mmol/l before meals and 3.5 to 10 mmol/l after meals, with a range of 7 to 10 mmol/l before bed and 3.5 to 7 mmol/l at dawn. Meals are also rigidly defined with a time and a carbohydrate content. A qualitative model is used to reason about insulin dose adjustments, insulin types are described by parameters of duration of action, onset and peak activity. This describes a piecewise smooth curve with three sections: a rise from onset time to peak time, a duration at the peak and a falling off section to total duration of action time. A limit of 15% is placed on dose changes. Similar piecewise curves are employed to estimate glucose predictions after meals. The expected modification of the blood glucose profile after adjustment of all available parameters is calculated and selection is made of the most appropriate therapeutic action to take. Only one adjustment is made at any one time.

First, the system attempts to select completely appropriate decision(s); if these cannot be found because the normalisation of one glucose value would be deleterious to another, these partially appropriate actions are suggested. If none of these can be found, then suggestions for modifying the whole regimen should be made to overcome the difficulties. In the present system insulin adjustments are limited to +2 or -2 units, a desirable development would be to take account of individual and circadian variations in sensitivities to various insulins used.

Three modules are defined: module one prescribes a diet dependent on age, sex, height (ideal body weight) and activity level in rather simplistic terms. Module two is an initialisation module for starting insulin therapy, this is apparently always twice daily injection of intermediate insulin unless an insulin dose regimen already exists. Module three is the therapy

optimisation module, or module for subsequent consultations as it is referred to in the paper, which may adjust any of the parameters of diet, timing of injections or meals, doses or the regimen itself as appropriate.

The information available appears to indicate that the system is too regimented and lacks flexibility for both patients and physicians; there has been no indication that a link to a patient monitoring device is a future aim of the system, although it would appear to be desirable in order to collect data in order to communicate with the stage three program.

Berger and Rodbard (1990) describe the CADMO (Computer-assisted diabetes monitor) system which has been designed for intelligent automated analysis and interpretation of data relevant to glycaemic control. This suggests that due to the complexity of interactions involved in glycaemic control and the lack of well-established straightforward rules for its interpretation, the optimal contribution of expert systems would be in intelligent data abstraction and presentation.

CADMO accepts data from standard memory meters and generates reports to discuss various aspects of overall glycaemic control, several alternatives are then proposed so that the clinician can then make the final decision. Program interaction from the keyboard is minimal, merely requiring the patient's name and weight, dates to be analysed and a target blood glucose value.

Information, which may be displayed one time point per line, includes glucose, insulin dose(s) and events (meals, hypos activity etc.). Statistics are provided of mean and standard deviation for total glucoses and for each time of day. Similar statistics are provided for insulin doses. Glucose may also be summarised by day of week and in non-parametric forms which display the percentage of results below or above threshold values - e.g. percent below 70 mg/dl (about 4 mmol/l).

Statistical tests are used to evaluate differences in mean glucose values within certain ranges or time periods, Student's t-test and the chi-squared test are used. The results of these tests are

then entered into rules which give textual responses to the user. These are triggered if mean values at certain times of day differ significantly from the overall mean for the whole period. Hypos (BG<50 mg/dl (approx. 3 mmol/l)) are checked for reasons such as larger than usual insulin dose or exercise. Finally, a summary highlights the points to be addressed by the physician.

In order to take this a step further and suggest insulin dose adjustments, mathematical modelling techniques are employed: A plasma glucose profile is estimated from the glucose results by extrapolation, a plasma insulin profile is calculated from pharmacokinetic profiles of the individual doses. These two are used as input to a simulator, the model derives the rate of glucose entry and utilisation, which is in turn fed back to estimate more appropriate insulin input to achieve optimal glucose disposal and control. Suggestions for dose adjustments and/or regimen adjustments are made for the physician to choose; risks of hypoglycaemia and advised extra monitoring times are given in the summary report, which may suggest stepped increments with frequent testing to confirm the right track is being followed.

Drawbacks of this system are the large inter- and intra-patient variability of model parameters, the assumptions of constant lifestyle and diet and the difficulties of explanation to patients of the need for extra injections.

REQUIREMENTS OF DIABETES COMPUTER SYSTEMS.

Now that an historical overview has been given and example representative systems have been described, consideration of requirements for new computer systems may be addressed. These requirements are based on the information gathered for the early sections of this chapter and in particular follow from the work done by Bergeler et al (1985). Three classes of management or decision support systems were described by Bergeler: Large, hospital-based data management systems; Individual physician or small clinic-based systems and patient-oriented systems.

Table 3.2 lists the general features of computer systems desirable to provide medical support for diabetes. It is not necessary that all these features are present in one program however. Features may be subdivided into those more appropriate to the overall functional requirement of the program and the type of hardware and software available.

Table 3.2 General desirable features of diabetes management computer systems

1. Documentation of therapeutical data + simple interpretation.
2. Rules for data analysis and estimation of effects of meals, exercise and illness.
3. Regulation of blood glucose by application of algorithms.
4. Regulation with adaptive methods and optimisation of parameters.
5. Process model of insulin-glucose system.
6. Expert system of therapeutical problems in diabetes treatment

Table 3.3 Required features for therapy management computers

1. Connection with patient computers.
2. Presentation and analysis of patient data.
3. Optimisation of therapy parameters.
4. Development and optimisation of the therapy program.
5. Management of all patients in computerised therapy (personal data, supervision etc.)

Table 3.4 Specific requirements of a large, clinic-based system

1. Data bank with all therapy data modified for use by other programs
2. Subprogram with a copy of therapy algorithms.
3. Process model of insulin/glucose system.
4. Capabilities for simulation of problems in diabetes treatment and optimisation of therapy parameters.

Table 3.3 gives Bergeler's list of desirable features of physician or clinic-oriented computers and table 3.4 gives specific guidelines for facilities of large hospital-based data management systems. In the following two chapters, patient-oriented and physician-oriented diabetes decision support systems are described. These chapters contain much more information about he individual cases

CHAPTER 4 - PATIENT ORIENTED INSULIN REGIMEN OPTIMISER (POIRO)

INTRODUCTION

In chapter one, the complex process of glucose homeostasis was described and the problems presented by diabetes, especially insulin replacement therapy, were introduced. This chapter examines decision making problems which occur with the use of insulin and introduces the hand-held decision support system, POIRO, which was developed in this project to provide advice on insulin adjustment.

The unusual aspect of POIRO is that it is employed in an area where human expertise is not usually available; i.e. to advise on *day-to-day* variation of insulin doses for insulin dependent diabetic outpatients. Intelligent decision support systems traditionally model an actual human expert's problem solving behaviour. POIRO puts into practice theoretical knowledge that had previously been infeasible to apply, due to the lack of availability of physician advice to out-patients. Even with the advent of computers and expert systems, advice availability has been restricted, until recently, due to problems of physically transporting the computer. The single, most important consideration of this system , therefore, is that it is portable; with current technology, this limits the program design in crucial ways which are explained later. POIRO has been evaluated both by simulation and in two controlled clinical trials. The methods and results of these trials may make a significant contribution to the discussion of evaluation and validation of intelligent medical decision support tools.

AIMS

The main aim of the system is to provide intelligent optimisation of an insulin regimen selected by a physician. In order to be successful in this aim, the system has to be acceptable to both physicians and patients. A second aim is to provide diabetes education for patients by showing them how insulin can be adjusted. Finally it is intended to show how formal evaluation methods

(i.e. clinical trials) may be used in the evaluation of an intelligent computer system. These aims are described in more detail below.

Intelligent optimisation of an insulin regimen. The primary aim of the system is to optimise a prescribed insulin regimen. That is, given types and times of administration of insulin formulations, to apply rules of therapy adjustment in order to produce optimal blood glucose control. Optimal blood glucose control is defined as the achievement of the lowest possible mean and variability of glucose measurements without producing hypoglycaemia. This is a subjective quantity and will vary between patients. The major reason for this variation is the large inter-patient variability in the perception of the lowest possible mean blood glucose which does not cause an unacceptable risk of hypoglycaemia. Some patients may prefer to aim for a slightly higher mean blood glucose than others in order to minimise the risks of hypoglycaemia. Factors which need to be considered in this decision are occupation, age and the presence of complications.

Physician acceptability. Physicians recognise that many patients currently give no consideration at all to decision making; they do not have the time, ability or motivation to sit down and work through calculations on how much insulin to inject on a meal to meal basis. Consequently, it is common for patients to remain on the standard doses advised, even when feeling unwell. Physicians are limited to making crude adjustments at irregular intervals; a safety-first policy may be adopted in which they do not attempt to optimise the therapy due to lack of evidence, or lack of confidence in the standard of education attained by patients. The incidence of both ketoacidotic diabetic coma (caused by uncontrolled high blood glucose) and hypoglycaemic coma (caused by excessive insulin dosage) is evidence that this *modus operandi* is unsuccessful for many patients. A decision support system for these type of patients which is easy to use, but provides physicians with capabilities to set individual targets and retain control of the rate at which insulin adjustment is carried out, should be aimed at; the system should relieve physicians of many commonplace insulin adjustment queries which may currently be made by patients by telephone between clinics. It is therefore essential that a control and

initialisation program is developed concurrently on a desk-top microcomputer. This controller program should aim for an equally intuitive and easy to use user interface in order to motivate physicians to use it.

Patient acceptability. POIRO is designed for people who have no previous experience or aptitude for computer devices and to provide a comfortable and intuitive system for them to use with confidence. Reasons why computer assisted insulin adjustment has not previously made much impact include the cost of suitable systems and ergonomic considerations, such as the small size of keyboard and display of portable computer devices.

Diabetes education. POIRO also aims to educate people in the art of self adjustment of insulin doses; this should be made possible by explanations of advice given where appropriate.

Formal evaluation. Previous computer-assisted insulin adjustment devices have lacked properly controlled clinical trials and this has affected their acceptability to practising clinicians. Ideally, the evaluation should be in two stages: the dose adjustment routines should be tested against computer simulated patients and then in clinical trials with real patients. The simulation studies, with appropriate choice of parameters should show how the dose adjustment algorithms cope with unusual circumstances and may give an indication of safe limits for frequency and levels of adjustment. Clinical trials demonstrate the effectiveness of computer-assisted insulin adjustment versus normal practice (albeit with the addition of a computerised logbook).

Requirements

Bergeler (1985) listed 14 requirements for the optimal patient-oriented therapy adjustment computer (table 4.1). This table forms an excellent starting point for defining requirements of the proposed POIRO system.

Table 4.1 Optimum requirements for a patient-oriented computer system for insulin therapy.	
1.	Small package and minimal weight.
2.	Large display and comfortable dialogue
3.	Large keys for safe operation.
4.	Minimum number of operating keys.
5.	Clock.
6.	Control capabilities for pump.
7.	Interface to blood glucose measurement unit.
8.	Adequate data exchange facilities.
9.	High calculating speed.
10.	Sufficient data storage capacity.
11.	Minimal power consumption, battery operation.
12.	Battery exchangeable without loss of data.
13.	Integrated hardware checks for malfunction.
14.	Program development by means of high level languages.

Two of Bergeler's requirements were not included in the original POIRO requirements specification: requirement 6 (because there is no patient filtering of the advice) and requirement 7 (although attempts were made to interface with the Exactech meter). One additional requirement of POIRO was security of both data and the program parameters. All these requirements are now described and justified in more detail.

Small physical size. As already stated, this is of paramount importance as people travel everywhere with their insulin and should be able to enter information at any time, and to receive insulin dose advice at any time. The only way this may be achieved is to have a device small enough to fit into a handbag, briefcase or pocket.

Large display. Mistakes in insulin doses read from the display may cause undesirable effects in the blood glucose; injection of 18 units of insulin instead of 10 could cause severe hypoglycaemia. Eye problems are common among people for whom the duration of diabetes is more than five years, therefore the size of text should be large enough for people with less than perfect vision to read with ease.

Comfortable dialogue. The display should contain sufficient lines of text to provide natural language prompts and advice. In the past, small screens have led to the use of abbreviations which patients have had to learn and may initially find confusing.

Large keys. Essentially a safety feature, "slips" (defined as errors in execution) are less likely in proportion to the size of targets. This is in accordance with Fitt's law (chapter 2, page 64) which states that the time taken for a user to move (a hand or pointing device) to a target depends on the ratio of distance moved to the target divided by the size of the target.

Minimum number of operating keys. This requirement assumes a fixed number of keys for entering data, rather like a calculator keyboard. The requirement may be modified for configurable screens which support menus to incorporate Hick's law (chapter 2) The requirement for POIRO may be stated as "minimise the number of options available at any one time in order to limit confusion and optimise selection time."

Clock. A timer is essential in order to relate events such as isolated blood glucose measurements to previous meals and insulin doses. Time and date stamping of all the events as they are entered assumes that they are entered at the time of measurement. It is not a requirement of the system to allow retrospective entry of information, except for hypoglycaemic reactions. It is required that all hypos are recorded as soon as possible; this is due to the importance of preventing further hypoglycaemic reactions if possible, it is also a requirement to permit retrospective entry of hypos as hypoglycaemia may prevent the patient from using the device at the time.

Control capabilities for a pump are not an immediate requirement of the system, although it may be possible to integrate the output from the system into an open-loop or even a closed-loop insulin pump in the future. Rigorous validation of the adjustment algorithms is essential before this step could be contemplated, due to the lack of validation by the patient and the medico-legal issues this raises.

Interface to a blood glucose measurement unit is not an essential initial requirement as data may be entered manually via a keyboard. In fact, an advantage of not having an integrated blood glucose meter is that users may continue to use their existing method of monitoring. For

a mass-production device, an internal blood glucose sensor is a more realistic and sensible requirement.

Adequate data exchange facilities. The capability to initialise parameters, such as insulin regimen and initial insulin doses, blood glucose targets and safety limits on a standard desktop microcomputer must be provided. Two way transfer of all data is essential. As the system is intended for use by physicians with limited experience of computers, the data exchange should take place smoothly and reliably, and it should be invisible to the physician and patient once it is initiated, preferably by the selection of a menu option or a key press.

High calculating speed. The device has to respond quickly in "real-time" to requests for advice. The performance in terms of delay times for screen display and insulin dose calculation should be minimal. The delays must not mislead patients into thinking the device is faulty or not responding.

Sufficient data storage Memory management needs to be organised so that the most recent events are kept in memory; once data storage is exhausted the oldest recorded data should be overwritten by new events. The progressive nature of type I diabetes is such that any data older than this is not relevant to the current state of the patient. As a rough guide, sufficient data storage may be defined as the amount of computer memory required to store all the events entered between visits to the clinic (approximately three months of data).

Minimal power consumption The device should not depend on access to the mains electricity more often than is convenient. Nickel cadmium based "Ni-Cad" batteries are currently the most efficient power sources which can deliver the level of power required to drive a portable computer, although in the near future lighter and more efficient lithium-based battery cells are likely.

Battery exchangeable without loss of data. This may be facilitated by a second "back-up" battery, which may be less powerful than the main battery as it is not required to drive functions

such as the screen, but merely to preserve the contents of memory while the main battery is disconnected, or in emergencies when it becomes discharged. Loss of data may also be limited by the use of a permanent data storage medium, such as a smart card or laser card (Brown 1989), and some small computers also now have small magnetic disks.

Integrated hardware checks for malfunction. This may be framed as a question: "is the device reliable in everyday use?", many commercially available computers check random access memory (RAM) every time they are turned on. If a problem does occur with the hardware, users should be notified in simple terms to discontinue using the device and to consult their physician for advice.

Program development by means of high level languages. This is a principled development feature and is desirable (although not essential) for documentation and maintenance of the system. High quality software engineering is becoming more well-defined and many development strategies have been defined. The waterfall model (Sommerville 1988 p7) has been the underlying methodology used for the development of this system. Methodologies designed especially for knowledge-based system development (such as KADS - Hickman et al. 1989) are also based primarily on the waterfall model. In terms of language choice, memory limitations often prevent the use of specialised artificial intelligence and object oriented languages such as Prolog, Lisp, SmallTalk and C++. The nature of the problem also affects the choice of implementation language. Prolog is suitable in ill-defined domains where much uncertainty is present: whereas well defined domains, such as insulin therapy, may be more suited to procedural modular languages such as C or Pascal. In the latter case, some crucial aspects of the problem may be expressed in algorithms. The choice of hardware may also limit the language choice due to the lack of memory and a lack of suitable software compilers for the underlying operating system. For programs written in safety-critical environments, Cullyer et al (1991) claim that Pascal is the safest choice of programming language due to its strong typing and integrated compiler checks.

Security. Access to the data transfer routines, and to the parameters of the dose adjustment algorithms must be protected by a password for ethical reasons. The password may be limited to a physician's identification or may be a general password which may only be generated by a hospital data base for example. Smart cards provide secure, password protected data storage and are an option for security of data as they are non-volatile and therefore less susceptible to hardware or software failure.

Prototype Development Device

Two options exist for a prototype system: either a device is custom built, to suit the design specifications, or a commercially available computer is chosen which provides the best match to the requirements. Advantages of a custom built device include immediate compliance with all the hardware requirements, whilst the disadvantages are the initial cost, delay in production and a lack of flexibility during the prototype software development. Advantages of the use of an existing programmable computer include immediate availability of the hardware and flexibility in programming; disadvantages include possible non-compliance with one or more of the design requirements.

At the outset of this project (in 1988), possible hardware choices were examined. With the above factors in mind the selection of a prototype development device could take place. Devices available which were considered (primarily because of criterion one - the small size required) included Hewlett Packard programmable calculators, the Sharp PC 1500 and the Epson EHT-10. Of these, the EHT-10 complied with all thirteen of the essential requirements outlined, thus eliminating the need for a custom device. It had by far the largest display (14 cm. by 7 cm. or 14 lines by 12 characters) and also benefited from the novel feature of using a touch sensitive screen in place of the conventional keyboard.

The problems of patient acceptability are eased by the use of an easy method of communicating information between the human user and the computer. Successful systems for everyday use

tend to spurn traditional typewriter-style keyboards and have special "one-touch" function buttons. This type of interface is now common in bank cash machines and in the graphical user interfaces (GUIs) used in the Macintosh™ and Windows™ operating systems. Another point to be made about successful computer systems is that the "computer" angle is often hidden from the person using the device, people are said to be less reticent about computer systems if they are unaware that they are using one (Essinger 1990). Even in simple, one touch methods of data entry, people still have confusion over the selection of the correct option (personal observations of people using cash machines). Technology provides a solution to the problem of relating between screen prompts and the correct button to press by the combination of the two in a touch-sensitive screen.

The EHT-10 was chosen for prototype development on the basis of these considerations and also because it has many of the functional capabilities of a standard microcomputer: it supports RS232 communications; it has 256 kilobytes of memory, and it has the ability to run compiled Turbo Pascal programs under its CP/M operating system. Turbo Pascal version 3.0 was therefore selected as the development language. The EHT-10's appearance is shown in fig 4.1. For full technical specifications see Appendix 1.

Features of the Device, Compliance with requirements.

The EHT-10 screen incorporates a grid of 70 touch-sensitive pads (5 wide by 14 long). These may be configured so that a number of pads combine to form a single touch-sensitive input area, the full width of 5 pads permits menu items of length 9 characters or less within a border. In this way, menu items are defined as demonstrated by the main menu displayed in fig. 4.1. A

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clock is available via in-line assembly code routines. An RS232 communications standard interface may likewise be accessed via in-line assembly code routines.

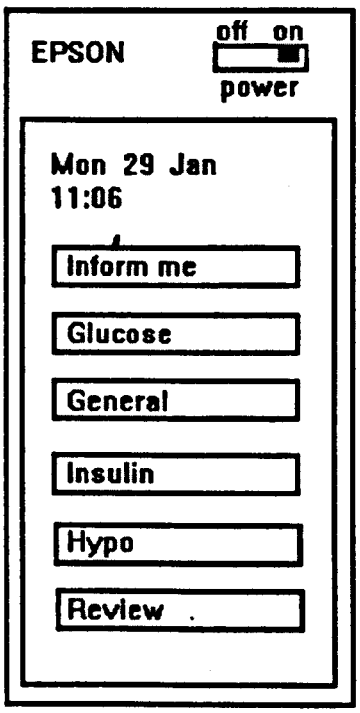

Fig 4.1 Diagram representing the EHT-10 hand-held computer, showing the initial screen of the prototype POIRO system

Part of the memory is utilised as a "RAM disc" which allows very fast access times (approx. 20 ns per access). Memory is divided into areas for program storage, program execution and data storage. Memory is allocated for program execution at compile time within Turbo Pascal; consideration of memory restrictions and the provision of sufficient storage space for data (see above) were important factors in the development of data structures and the program code.

The EHT-10 may be programmed directly using a plug-in keyboard but a second option was used for development of the POIRO software. The code was written and tested on a conventional desk-top PC before compiled code was transferred to the EHT-10 for testing. The development cycle required that code was recompiled after substituting files containing machine-specific code to call the user interface, communications port, and clock.

The Ni-Cad battery cell requires mains charging, on average, once per week in normal use. In order to conserve battery power, the computer has an automatic "sleep" function which turns off the screen after a pre-set time in which no data entry takes place (this may be set by the user). However, even momentary power loss, or errors in the program which cause the system to reset, deletes the program and destroys all the data stored on the RAM disc. Two methods are available to alleviate this problem. The program may be stored in a computer component known as an EPROM (Electronic Programmable Read Only Memory) which is plugged into the circuit board of the device and is protected by the operating system of the computer; this is only cost-effective for large-scale use of the program. Secondly, a smart card can be utilised as a non-volatile data storage unit. Smart cards are under intense research and may become a useful method of storing patient notes; limits on data capacity and speed of access are drawbacks of present smart card technology but these should be overcome in the near future. Routines for using the smart card interface were implemented and smart cards were used for around ten percent of patients during clinical trials with the POIRO system.

Attempts were made to integrate a glucose meter (the Exactech™ "pen") with the EHT-10. The meter was connected to the printer socket on the EHT-10 and software and hardware were developed in an attempt to capture the output from the meter and to decipher the signal for display on the EHT-10's screen. The integration was unsuccessful due to the speed and non-standard format of the stream of data obtained from the output of the meter in relation to the data entry capabilities of the EHT-10's printer socket, although a routine to capture and decipher the data was successful on the development PC. Therefore the integration of a blood glucose meter had to be postponed in favour of other developments, but a commercial system would undoubtedly benefit from this connection.

FUNCTIONAL SPECIFICATION

Detailed specification of the functionality of the POIRO program is now presented. It was decided that the prototype should be developed in two stages: the first stage was to include the definition of data structures and subsequent implementation of a data collection utility, while the second stage would include the development of intelligent dose adjustment and general advice functions.

During stage 1, code and data structures for displaying textual prompts on the screen had to be defined. The factors that are known to affect blood glucose control had to be data entry options and these options were to be allowed to be entered individually at any time. In the development of data entry screens, medical jargon had to be avoided and the language as natural as possible. The design had to make it possible to provide individual language definitions for patients with different concepts (of meal-times for instance). Data structures for storing the screen text had to be defined so that the language (initially English) for the text of

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the screens was completely separated from the program code. This enabled the text to be translated into other languages for use by non-English speakers in this country or in other countries.

A clock provided a facility to record the time and date of all data entries, known as *events*. Methods of storing events had to allow flexible access in order to retrieve previous events for use in the dose adjustment algorithms. As space was limited, the data had to be stored such that the most recent events were available. Therefore, in cases of memory exhaustion, the oldest data was sacrificed to free memory for new events. Patients had to be able to review personal data, such as their next clinic time, as well as all the data they have entered. In addition, they had to be able to see graphs of glucose values in order to observe trends in their control. Methods of recording information wer to be kept simple, so that patients did not have to do any complicated calculations before entering the information, which was to be recorded with a minimal amount of key presses.

The initial development of an unintelligent data collection device was necessary for two reasons: one was to test the feasibility of the use of the hardware by patients, and the second reason was that the routines for suggesting insulin adjustment needed to be separated from the functionality of the interface and data storage. This requirement is analogous to the separation, in traditional expert systems, of the inference engine and the knowledge base.

Data transfer routines had to be incorporated for data to be transferred to and from a desk top computer under the control of a physician. The initial requirements of the initialisation program were that it connected to POIRO simply, reliably and securely (secure in terms of password-protected access) in order to transfer initial parameters of the system (defined below) and to send and receive data from it. Subsequent archiving of data collected using POIRO for further analysis and long term storage also had to be provided. Interpretation and statistical analysis routines were to be added to the physician's program in stages once these essential functions were provided.

Once stage 1 had been successfully completed, the second stage of development was to provide active decision support. After completion of the second stage, POIRO was to be able to suggest insulin doses when requested and to provide unsolicited warnings and advice, when appropriate, in response to the information entered by the patient. Warnings were to be displayed, for instance, if blood glucose entries were not within predefined limits, or if an insulin dose is requested at an inappropriate time (e.g. within three hours of the previous dose for short acting insulin doses). However, the major decision support function required was the suggestion of insulin doses. An insulin regimen was to be selected by the physician and initial estimates of doses wer to be provided. These doses were then to be optimised in response to glucose levels and insulin doses taken from day to day. The *standard* insulin dose is a term applied to the dose of any insulin, that is normally advised by a physician at a clinic, which would be taken in standard circumstances. Where non-standard conditions applied, supplementary insulin had to be calculated and advised if appropriate. Any changes from standard doses were to be explained to the patient upon request . The insulin option was to include a facility for over-riding POIRO's suggestion, i.e. the suggestion was not to be made dogmatically. Where patients decided to alter the advised dose, the dose actually *taken* had to be recorded and used to assess the correct dose the next day.

A major requirement of the system was that it should be tolerant of missing data. Missing data means, in effect, missing blood glucose values, although the system was also to be tolerant of unavailability of other information. It would be unrealistic to expect completely regular daily blood glucose monitoring and it was thought that most patients would probably appreciate a system in which regular (four times per day) blood tests were not required every day.

At various stages during the development, patients were able to use prototype systems for evaluation and feedback. This provided some user requirements which had not been included in the original requirements specification. For example, an additional feature requested by patients was a free text facility to enter events not covered in the system, or to add short

explanations of unusual events, as is often done in existing log books (such as the explanation of a high fasting blood glucose by the patient's having missed the previous evening's ultralente dose). Similarly, there could be many explanations for hypos other than an insulin dose which was too large.

The next two sections describe the detailed design specification and implementation of the above functional specification.

STAGE 1 - FEASIBILITY AND DESIGN OF A DATA COLLECTION FUNCTION

The first stage of the design involved the definition of appropriate data structures: (a) for screen text and menu options, (b) for storing general information about patients, their blood glucose targets and their insulin doses, (c) for the events which may affect the blood glucose, (d) the blood glucose itself and (e) a facility for free text entry.

Text used within the system was divided into *screens*, each with a code number. The data structure for a screen is shown in fig 4.2, a variable number of lines of text, together with the x and y coordinates of each line's placement on the screen, is followed by an optional set of menu options (a limit of four selections is set in order to keep the menus short and simple) and an optional string of text for units if appropriate. All the language is initially entered in plain text in a standard ASCII text file in a defined syntax (see Appendix 2). This file is read into the computer's memory when it is first switched on. These structures allow screens to have an unlimited number of lines of text and makes possible the conversion of text into any language with the restraint of screen size and word length in the language. The EHT-10 has 12 optional character sets for characters with special accents in other languages apart from English. The language to be used may be preselected by the physician at the time of initialisation.

x_position	column on screen where text appears
y_position	line on screen where text appears
line	text to appear
next_line	pointer to the next piece of text
first_line	pointer to first piece of text
option_list	array of up to four menu options
units	units text for an event

Fig 4.2 Data structures for screens.

The patient identity data structure is shown in fig 4.3, it incorporates an identification number which is used to identify records stored on disk for the patient, it is probably wise, although not essential, that the identity number should be set to the patient's hospital number. In the current prototype, the number is set by the physician with the POIRO managerial program (PMP) which is described later. A check is made to see if the number has been previously assigned to another patient and if the patient named is already registered with a number. For any future wide-scale use this would need to be standardised so that a standard core set of reference data could be used for identification. This might include date of birth, sex, nationality etc.

surname	surname used to link to database
first_name	
id_number	hospital number set up by physician
gender	0=female, 1=male

fig 4.3 Patient identity data structure

Three data structures are defined to store therapy-related parameters (fig 4.4 to 4.6). All these data structures are listed at this stage even though some parameters within the structures relate to dose adjustment and are used in stage two of the design and implementation. The function of each of these parameters will be explained as the need arises.

Information about height, weight, diet advised and physical fitness are stored in the first data structure (fig 4.4), these are all standard items already recorded in diabetic clinics; the items are for information only and are not used in any of the dose adjustment algorithms or for giving advice. The second data structure stores target blood glucose levels and permitted differences

from the expected levels before dose alteration will take place (fig 4.5). The third data structure stores dose prescriptions set by the physician and limits to which the doses may be changed by the system (fig 4.6).

height	height in cm.
weight	weight in kg.
calories	total daily calories of recommended diet
carbohydrates	total grams carbohydrate in recommended diet
fitness	fitness level, on scale 0 to 100
doctor	physician's name
phone	emergency contact number
phone_2	second emergency number (for nurse during trials)
clinic_date	date of next clinic appointment
clinic_time	time of next clinic appointment

fig 4.4 Data structure for general information

target_BG	default target fasting blood glucose
maximum_BG	limit set by physician for clinical safety
minimum_BG	lower limit for clinical safety
risk_level	number of standard deviations
allowed_offsets	permitted mean offset set by physician
reference_curves	standard meal excursion reference curves
mean_offsets	moving average mean glucose offsets
last_offset	last calculated offset
current_offset	present offset
offset_date	date of last offset calculation
number_offsets	number of offsets calculated since last dose adjustment
mean_BG	moving average pre-prandial blood glucose array
variance_BG	moving average variance of pre-prandial blood glucose array
total_BG	total number of pre-prandial blood glucoses entered array

fig 4.5 Data structure for blood glucose-related information

insulin_types	types of insulin: short, intermediate and long
initial_doses	doses set by the physician for each type
last_dose_long	time of day of last long acting dose
current_doses	current (derived) doses array for each type
maximum_doses	maximum permitted doses set by physician
minimum_doses	minimum permitted doses set by physician
multipliers	supplementary insulin multipliers array

fig 4.6 Data structure for insulin dose-related information.

The blood glucose test results and influential factors which affect the blood glucose level all need to be recorded by the system. An event is defined as a timed data entry, a minimal amount of specific information is stored for each event in addition to the time, date and time of day of the event. The time of day relates to meal times, the four time points are breakfast, lunch, dinner and bedtime. When events other than meals are recorded they are attached logically to a time of day or are recorded with the time of day set to "uncertain". Fig 4.7 shows the event data structure. The date and time of the entry are recorded in conventional character string format as day/month/year (e.g. 28/03/90) and hour:minute (e.g. 12:30) respectively. The event code links to the language file and records the screen from which the event was entered; it is used to locate events of a certain type from within the store of events.

event_number	e.g glucose = 2, insulin = 4
date	in format "dd/mm/yy"
time	in format "hh:mm"
choice	number of selection from menu of options
value	e.g. BG level, dose taken
value_2	e.g. moving mean BG, dose advised
value_3	e.g. moving variance BG, standard dose
time_of_day	0=breakfast, 1=lunch, 2=dinner, 3=bedtime, 4=other time

Fig 4.7 data structure of an event

Some events require a numerical value to be explicitly entered (e.g. a blood glucose value, or insulin dose) while values for other factors may be represented on a 1 to 4 scale after being entered symbolically (e.g. size of meals, intended exercise). The selection of items from a list of options (menu) was used wherever possible in order to simplify the system as patients often

have limited keyboard skills. Two additional fields are provided for various extra information and calculations relevant to the event, such as an updated moving mean and moving variance for glucose measurements; for insulin events these fields store the usual (standard) and advised doses. This coded information may be decoded at the clinic appointment by the physician using the POIRO manager program (PMP) and displayed with the original text of the screen.

The recording of a measured blood glucose is defined as an event. The level of blood glucose measured by current blood glucose testing devices may range from 1 mM up to 30 mM. Many meters however have a limited range of possible values which is within these limits; if the blood glucose is very low or very high, these meters often display a text warning in place of a numerical value. The major quantities which affect the blood glucose are defined in the indented knowledge table below (table 4.2).

Table 4.2 Factors which affect blood glucose

Blood glucose depends on:
- Time of day
- Meal size and composition
- Exercise
- Health
- Insulin

The quantities of Table 4.2 are defined as individual event options, with the exception of meal composition. Whilst it is acknowledged that the composition of meals does have an effect on the blood glucose (Schrezenmeir et al 1985a) these effects are not well understood and are thus difficult to include in a decision support system of this size without the addition of severe complications. It is accepted that the major effect on glucose level is the actual portion size of the meal and its timing (knowledge acquisition from knowledge tsar).

Circadian variation of insulin requirements were investigated by Schrezenmeir (1985a) who consistently found that glucose levels rose higher at breakfast than for other meals. It is therefore necessary for the time of day to be entered in some way, as insulin doses vary with each main meal. Four times of day were defined, based on the four usual times of insulin

doses: these were morning, afternoon, evening and bedtime. A screen was implemented which prompted patients to enter the current "time of day" before entering any events. This proved too confusing for patients and did not allow for events to be entered at other times, for instance a blood glucose test mid morning at .the time of taking a snack. The time of day concept is closely related to meal-times, therefore patients in fact need not explicitly enter a time of day but merely which meal is about to be taken: the options are Breakfast, Lunch, Dinner and Snack. Note that there is no explicit bed-time in this classification as a snack is always recommended at bedtime, especially when insulin is injected at that time. This was much more acceptable and did not cause any confusion once it was made clear to people which time of day went with which meal definition.

A patient-oriented, relative system of recording events is used for meals, exercise and health. In the past, systems have requested dietary carbohydrate content of meals, either in grams of carbohydrate or bread exchange units (Schrezenmeir et al 1985a,b). Dieticians have now realised that these systems are too complicated and are misunderstood by many patients and some physicians (Eeley 1991). The two most important dietary considerations are the regularity and nutritional balance of meals - these are best monitored by physicians or dieticians in personal consultations. The only factor left is the meal portion size. A system of relative recording of portion size is now recommended by dieticians: In this new system, portion sizes may be recorded as "Nothing", "Light", "Normal" or "Large". These categories are therefore used as meal event options and are coded within the algorithms on a 1 to 4 scale.

As with diet, exercise levels may be recorded as "None", "Minimal", "Normal" or "Heavy", coded on a 1 to 4 scale; Health may be recorded as "Well", "Unwell" or "Very ill", coded on a 1 to 3 scale. In all three cases, normality is what is normal *for the individual patient at the particular time of day*. This should make it easier for patients to decide what entry to make.

Hypoglycaemia is a consequence of insulin therapy. Although the occurrence of hypoglycaemia does not directly affect the blood glucose *per se*, patients who have hypos may take some

glucose to counteract the hypo and this affects the blood glucose at the following measurement. Therefore Hypos have to be recorded as an event as soon as possible after they occur. People may be incapable of entering information when they are experiencing a hypo so retrospective entry of this event must be catered for. This is done by allowing a time delay since the hypo occurred (in hours) to be entered; this time delay helps to pin-point the insulin dose responsible for the reaction. In addition, each hypoglycaemic episode requires selection of a grade which defines the severity of the episode in terms of the assistance required to regain a more normal blood glucose level.

In order to meet the requirements for presentation of information to patients, the options "Review" and "Information" complete the event options. Review has three choices: "Readings" steps back through all events entered already, while "Values" and "Trend" display glucose readings in an interpreted graphical form

Unusual events, and explanations applicable to any of the events defined above may be entered in free text format in a data structure called the notebook in POIRO. In order to preserve memory space, the maximum amount of free text which may be entered by patients per notebook entry is 24 characters, i.e. two lines of text on the screen.

date	in format "dd/mm/yy"
message_number	integer record number
message	text of message (24 characters)

Fig 4.8 Notebook data structure

The notebook data structure is shown in fig 4.8. Notebook entries are stored in a rolling file similar to the event file; at the same time a notebook *event* is recorded in the event file; this contains a reference number (or key) to the notebook entry in the notebook file.

All events are finally entered by the patient via a confirmation option; if for any reason the patient does not want to enter an event once the screen has been selected, an abort function is

available. These functions are enabled in POIRO by two function keys situated in a standard position at the bottom of the screen and labelled "Ok" and "Quit" respectively.

An event which is not entered by the patient is the clinic event; this is recorded at every session where POIRO is connected to a physician's PC running the PMP. The event records whether the advice function was enabled or disabled, the position in the data file of the event and notebook pointers (i.e. the next position to be filled, which is equivalent to the number of events and notes recorded) and whether data was transferred to the PC.

The design of the data transfer routines was based on a protocol designed for use with a BBC microcomputer (Walter 1988). The protocol was modified in order to provide a password from the PC to POIRO and to define different block sizes of data for each of the files of information to be transferred, i.e. the patient data, events and the notebook. Full specification of the data communications routines are given in appendix 3.

IMPLEMENTATION - STAGE ONE

The software is predominantly written in Turbo Pascal. A few machine code routines were embedded in the code in order to use the special features of the EHT-10 i.e. the touch screen, beep, smart card, graphics and communications. A highly modular approach was adopted: procedures and functions were designed and written for each type of insulin separately. The code has been designed so that a limited number of input options are available to the user at any one time. Given that this is the case, exhaustive testing of every possible input should be possible, see later under evaluation and validation.

A set of EHT-10 emulation routines (to display a "screen", enable touch pads and beep etc.) were implemented in order to permit code design and testing on the development computer (an IBM compatible PC running MS-DOS). These machine-specific routines were separated into a source code "include" file. The EHT-10 specific routines to actually utilise the computer's functions were substituted for the emulated routines and the source code was re-compiled under

a CP/M version of Turbo Pascal. The executable code was created in command file (.COM) format and transferred to the EHT-10. The "End-address" (see Turbo manual) of the code under CP/M was set to D000 (Hex) in order to protect the BIOS routines and to leave room for data on the stack at execution time. Full documentation of the development methods and a complete listing of code and flow diagrams are provided in the POIRO documentation (Smale 1990).

The data structures defined above were implemented as record structures in Pascal. For maximum clarity of the main screen (fig 4.1), the number of options available from this initial screen was limited to 6, spaced one line apart. The description later outlines the method of use of the POIRO system.

Within events, the system of selection from a menu of up to four options was implemented as a grid of textual input boxes. The size of these touch-sensitive areas was, in almost all cases, standardised to the width of the screen (9 characters) by one character deep (approximately 5 cm by 1 cm). All touch pads which may be selected are displayed within a border for their easy identification and where selections are required the selected box is displayed in inverse (white on black) on the LCD screen. In all cases the selection is confirmed by pressing "Ok" or aborted by pressing "Quit" at the foot of the screen.

The order of execution of the main program is shown in fig 4.9. Initialisation involves the setting up of the text screen system, the patient related parameters and the opening of files for events and the notebook. If any of this information is not present, POIRO displays a message and waits for the data which should then be transferred from the physician's PC using the POIRO managerial program. The order of entry of data is recommended to be in the order glucose followed by general followed by insulin in normal circumstances. Logic is included to check and prompt for glucose and general events before insulin may be advised. It is impossible to obtain an advised insulin dose without first entering a meal time; other events,

however, are not mandatory. Complete program flow diagrams are in the POIRO program documentation (Smale 1990).

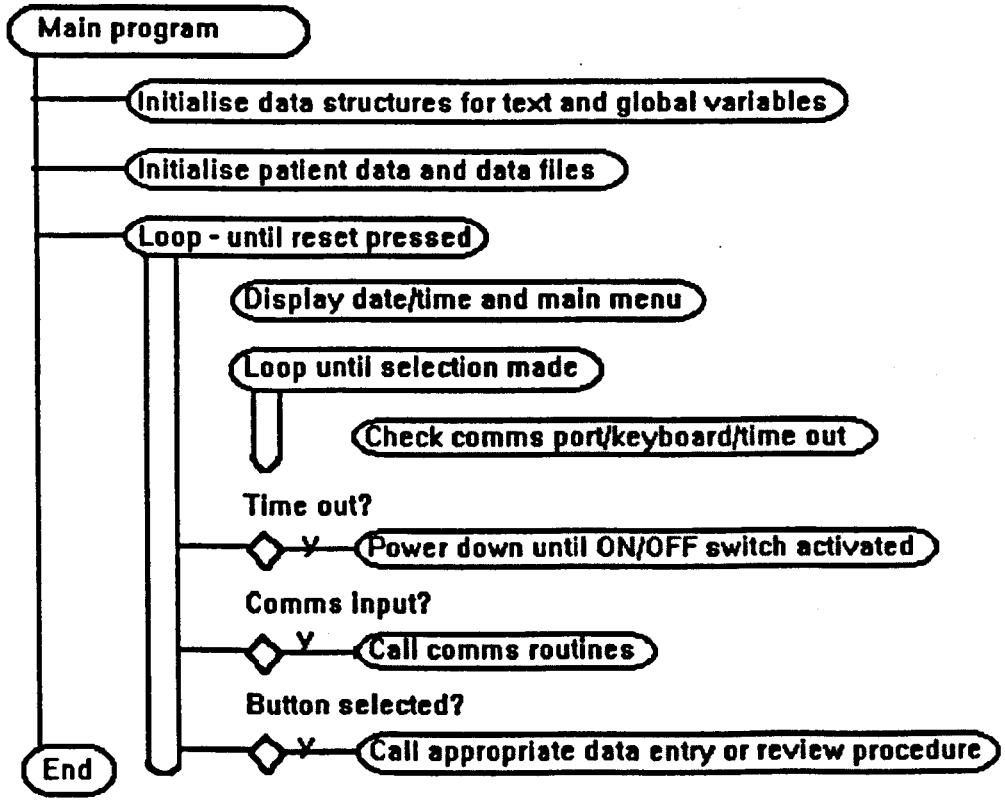

Fig 4.9 flow diagram of the main program cycle.

OPERATION OF POIRO.

When first turned on, the current date and time are displayed along with six major headings on touch sensitive pads: INFORM ME, GLUCOSE, GENERAL, INSULIN, HYPO and REVIEW. The procedure which occurs when each of the headings is pressed is described below.

INFORM ME displays a screen showing the patient's name, physician's name and telephone number(s) for emergency contact, the date and time of the next clinic appointment.

GLUCOSE sets up a calculator-styled numerical keypad which patients use to enter their blood glucose readings. There are two separate pads for entering a "Lo" or "Hi" reading, i.e. a reading which falls outside of the range of the blood glucose meter.

GENERAL prompts for four pieces of information: The meal time and relative size of the meal, plus the relative amount of exercise intended in the period following the meal and the health. Mealtime options are Breakfast, Lunch, Dinner and Snack. Possible meal sizes are *Nothing*, *Light*, *Normal* and *Large*; exercise amounts are *None*, *Minimal*, *Normal* and *Heavy*, health may be entered as *Well*, *Unwell* or *Very Ill*.

INSULIN allows selection of any of the prescribed insulin formulations and then displays the standard dose, the advised dose (when advice is enabled, see below) and the dose taken. The dose taken is set to the advised dose at first but may be altered by pressing the arrows to increase or decrease by one unit at a time if required. With the advice function enabled, the *Explain* heading may be pressed to display the information used to calculate the given dose.

HYPO: This option is used to record hypoglycaemic reactions. It includes a list of possible grades and a numeric keypad for entering a time delay in hours if the reaction occurred when the patient was not in a position to record it immediately. The patient is instructed to grade hypos according to the degree of intervention necessary to alleviate symptoms and regain normal blood glucose levels: grade one if the patient was able to cope alone; grade two if

intervention of another person was required and grade three if medical intervention was necessary. Fig 4.10 shows data entry screens.

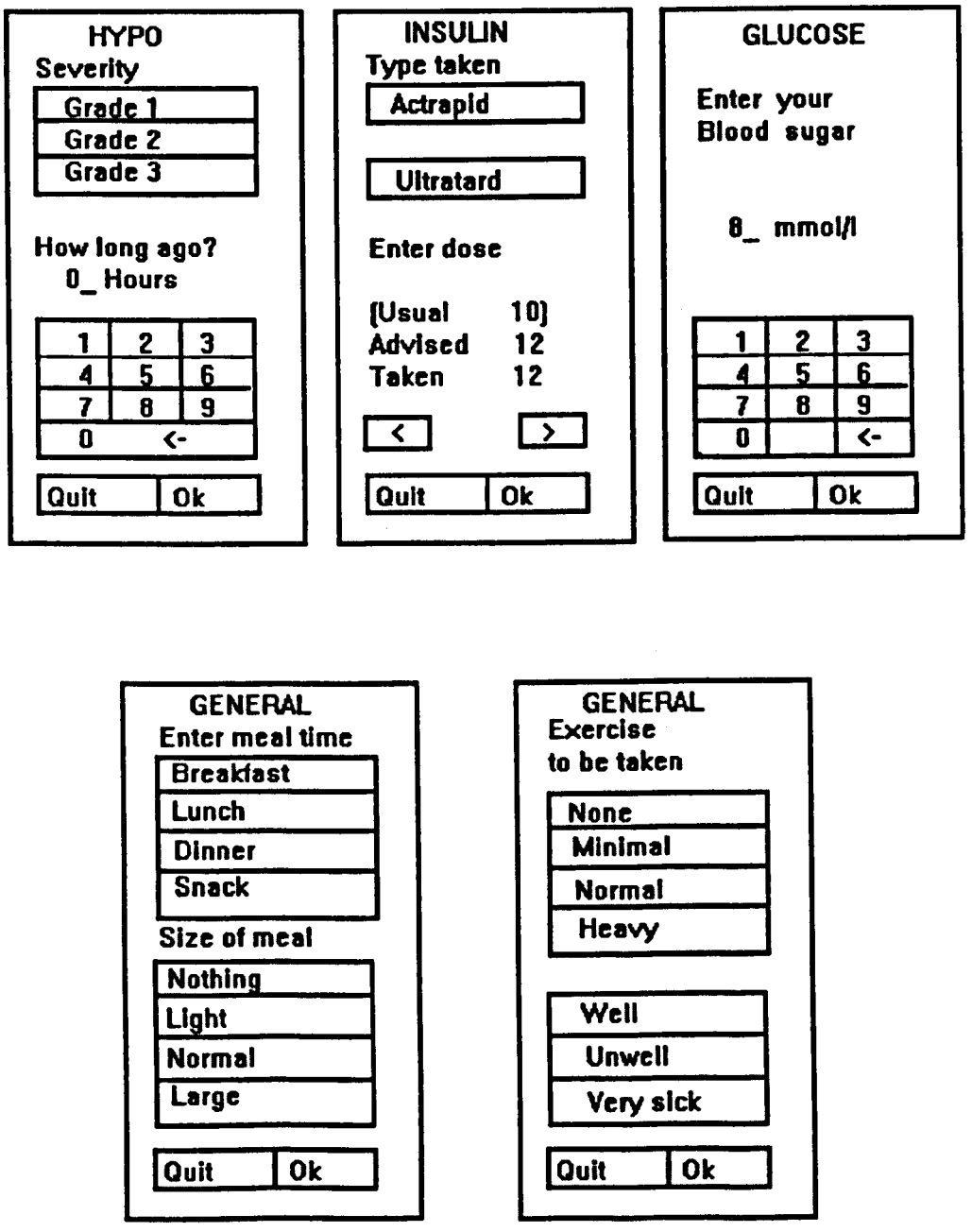

Fig 4.10 POIRO data entry screens. From top left: Hypo, Insulin, Glucose, General (meal) and General (exercise/health).

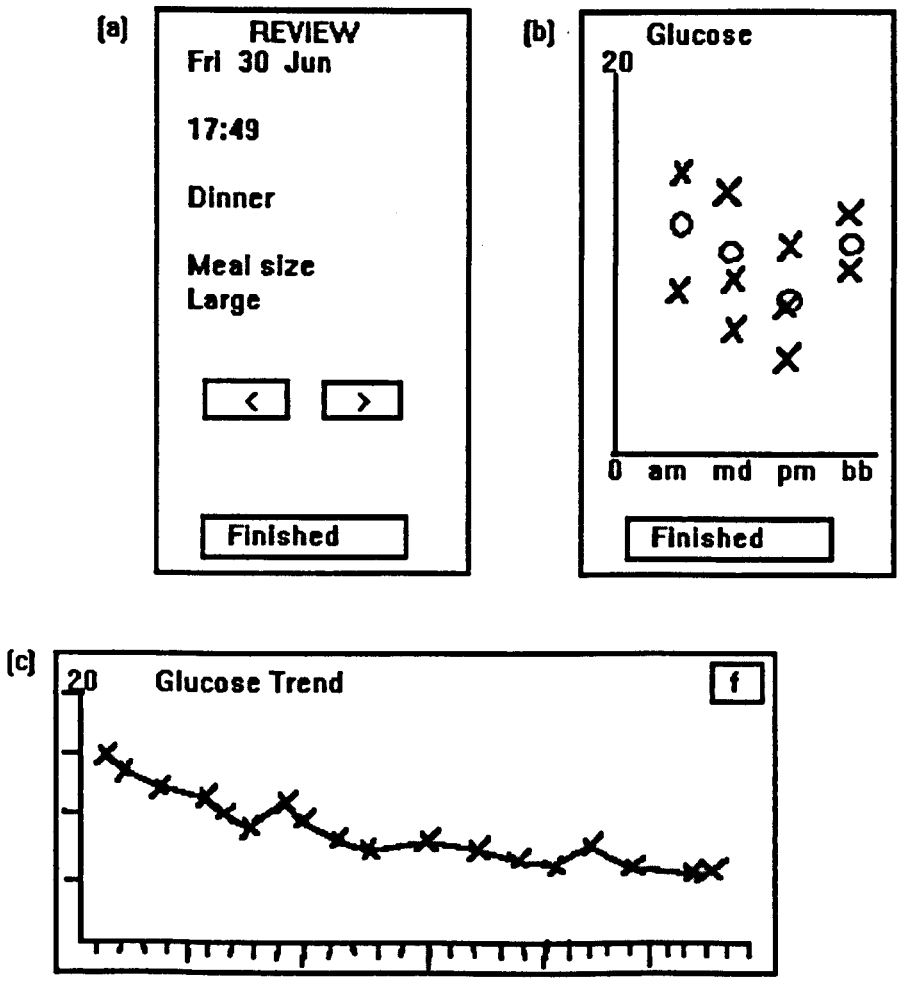

Fig 4.11 Review screens (a) Readings (as entered), (b) Plot of Values plus their Mean for each time of Day - traditionally known as a "modal day" plot and (c) Trend of Mean Daily Glucose

REVIEW is the option which permits the patient to view all the information previously entered in text form or as two graphs which show glucose control (Figure 4.11). The "Values" option displays all glucose tests entered for the previous week, in relation to the time of day, along with the mean of the values for each time of day; "Trend" displays the trend of mean daily glucose over the previous four weeks.

At regular stages during the data collection development stage, patients were invited to try the system and suggest any alterations or developments they would like to see. These initial feasibility trials were successful in terms of the positive reactions received from the subjects involved; requests from them were considered as an important part of the knowledge elicitation process; it was acknowledged that as patients were the eventual users of the system, it was vital to test their reactions throughout the development.

STAGE 2 - THE ADDITION OF INTELLIGENT DOSE ADJUSTMENT

The underlying concepts of insulin adjustment are well-defined but are complicated by the multiple factors which have to be considered. As stated above, the most significant of these factors are the size, composition and timing of meals, the amount of exercise to be undertaken following each meal, the prevailing blood glucose at the time of the meal and the general health of the patient. All these factors affect insulin requirements, although the relative contributions of each factor are not easily identified. Even after taking all these factors into account, insulin needs vary with the duration of the disease in ways which are not yet fully understood (Sharp et al 1987); this means that insulin dose adjustment is a perpetual process which does not cease once good control is achieved. The effects of changes in the liver, kidneys and other organs involved in blood glucose homeostasis mean that even so called *standard* insulin requirements vary, and therefore doses have to be monitored and adjusted throughout patients' lives.

The basic control model of glucose metabolism has one dependent variable - blood glucose - and one independent variable which has to be estimated - insulin. The other independent

variables may be predetermined to suit the individual concerned at a particular time. The equation for calculation of a post-prandial blood glucose value may be represented in general terms by equation E4.1.

$$G(t+\delta t) = f\,(\,G(t),\, M,\, E,\, H,\, I,\, t,\, X\,) \qquad \text{(E4.1)}$$

where G(t) is glucose at the time t measured before the meal or insulin dose, δt is an increment of time, M is the meal size, E is the intended exercise, H is the current health, I is the insulin dose taken and X contains any other possible factors such as injection site variability. In practice, a rearrangement of the function is required to estimate an appropriate insulin dose (I) in order to give a desired blood glucose (G) at time $t+\delta t$. Not surprisingly, no one has yet successfully defined such a function. The major problems lie in the complex interaction of insulin formulations (with differing durations), isolation of the individual components of the equation and the high variability between patients.

Metabolic simulation models have sought general functions and have achieved some success with modelling glucose-insulin dynamics (Rudenski 1987). This has mainly been in clinical research within the laboratory setting with carefully controlled parameter values: e.g. fixed food intake, same injection site for every injection. Metabolic models remain a region of great interest (Andreassen 1990, Jensen 1990) but their use to predict blood glucose in individuals in the outpatient setting is dependent on many (at the moment) unsubstantiated assumptions. Such models are, however, extremely useful for education of physicians and patients of the likely effects of changing any of the model parameters. Another use for metabolic models is as an alternative to clinical trials for evaluation of other dose adjustment methodologies. This facility has been utilised for evaluation of the present system and is described later.

Although all physicians are assumed to know and understand the processes involved in metabolic control, expertise in insulin therapy adjustment is traditionally acquired by practice, without a specific metabolic model in mind. Because of the system's complexity, rules of thumb have to be employed to estimate the effect of each of the factors mentioned above and

these rules, or algorithms, are learnt during clinical practice in a teacher-pupil relationship. Expert physicians who have mastered these rules are capable of achieving tight control in many patients, but are often frustrated by a lack of information and non-compliance from patients. With a computerised decision support system, such problems need to be addressed and the rules used by experts in all situations need to be included. In order to deal with uncertain or missing information, novel ideas are outlined later which go some way towards the promotion of tight control in all patients.

Theoretical Basis and Knowledge Elicitation

Selection of an appropriate insulin regimen for an individual is not within the scope of POIRO, but is addressed in the clinic decision support system described in chapter 5. However, rules for therapy adjustment are inexorably linked to the insulin regimen. For simplicity of development, one insulin regimen is selected and algorithms are defined to optimise the chosen regimen. The two most popular insulin regimen are the basal prandial regimen and the soluble isophane regimen, both are described in chapter 1 along with their advantages and disadvantages. The basal prandial regimen was chosen to be implemented first on POIRO. The reasons for this decision are that the regimen separates completely the background insulin requirements and the requirements to cover meal-times and that it more closely approximates physiological insulin production. Also, for purely practical reasons, the basal prandial regimen was more suitable for clinical trials as the majority of patients available for clinical trials were already following the regimen.

Optimisation of the basal prandial insulin regimen may be separated into two stages; the aims of these stages are: first, produce a normal fasting blood glucose by once or twice daily injections of long acting (ultralente) insulin; second, regain the pre-prandial blood glucose level by the time of the following meal. by injections of short acting (soluble) insulin. In addition, the regimen is flexible; it may allow supplementary short acting insulin adjustments for non-standard food, exercise and health.

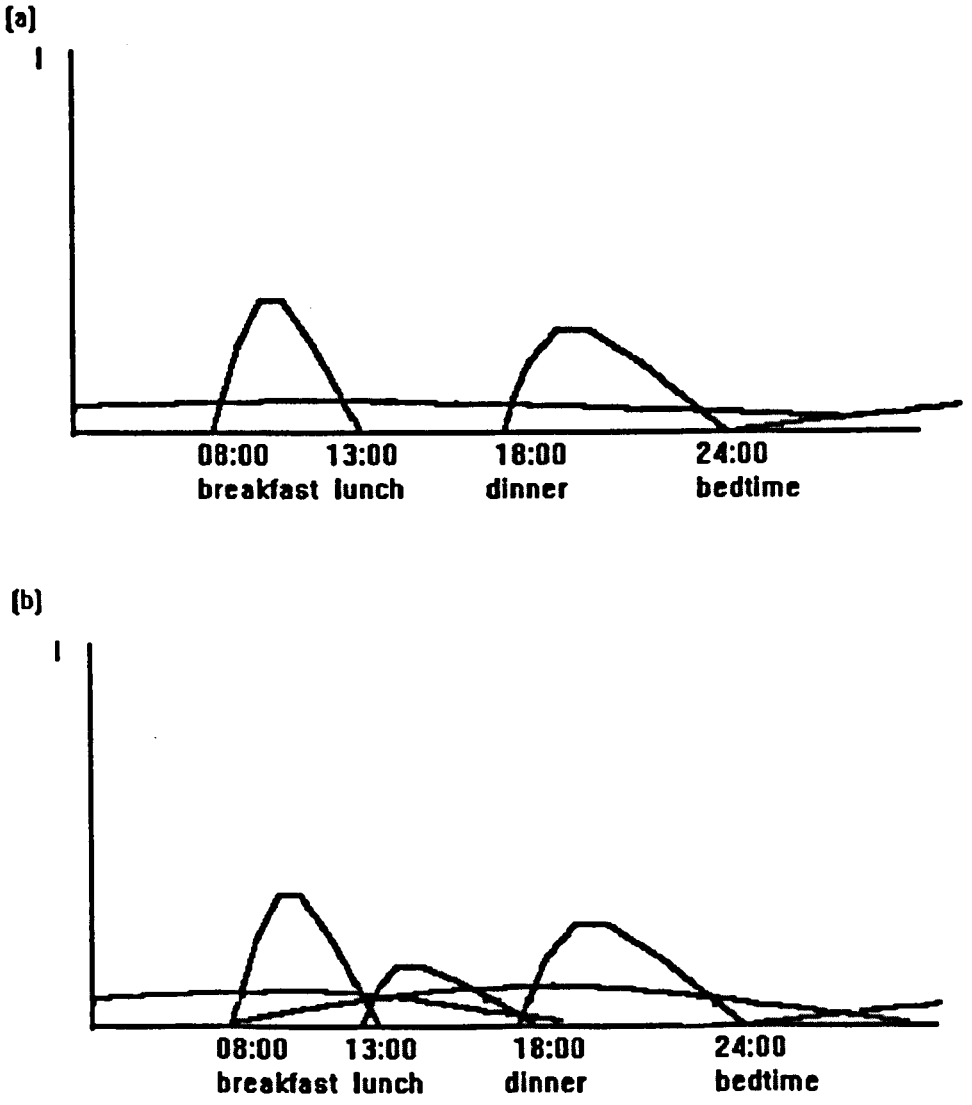

Fig 4.12 Basal Prandial regimen - possible variations: (a) No dose at midday, (b) Split ultralente dose

vertical axis (I) is insulin level in body, times on horizontal axis are for examle only and do not imply that meals have to be taken at set times.

Possible variations of the basic basal prandial regimen are shown in fig 4.12. Fig 4.12(a) shows the case where no dose of soluble is taken at midday, this is common for patients who have had diabetes for a short duration (less than two years or so) and those who eat only a small amount for lunch. The variation shown in fig 4.12(b) shows a split ultralente insulin dose, in this case half the total dose is taken before breakfast and half with either the evening meal or before bed. The split ultralente option is common among unstable (or "brittle") patients and those in whom the fasting blood glucose remains high despite a higher than usual basal dose. Further variations are possible, although the number of ultralente injections is never more than two per day and it is rare for short acting insulin to be prescribed more than three times daily, unless a very large bed-time snack is eaten in which case the limit is four injections per day. POIRO is capable of recognising any of these options and is flexible enough to optimise the chosen regimen.

Heuristic Rules

Insulin dose adjustment is not an exact science and is often described as an art (Fieschi 1990). It is not surprising, therefore, that heuristics, defined in chapter two, are the most common methods used by physicians in order to decide on the best treatment for diabetic patients. Therapy rules (or algorithms) for adjustment of insulin take account of the factors mentioned above and use long term information of responses to insulin doses to optimise the blood glucose values.

It is surprising, given the scope for variation in regimen and optimisation techniques, that relatively few sets of rules based on heuristics have been published (Skyler et al 1981, Chanock et al 1985, Shipp and Snyder 1986). These three algorithms have been compared with each other via computer simulation (Newman 1987); and comparisons have been carried out individually in which patients followed rules for periods with and without computer assistance (Schiffrin 1985).

In the simulation comparison by Newman (1987), the success of each algorithm was defined both in terms of the mean glucose produced and the number of hypoglycaemic reactions (defined as blood glucose < 60 mg/dl (3.3 mmol/l)). The study looked at the effect of variations in the model parameters used to simulate the natural trend and variability of blood glucose on the actual mean blood glucose and incidence of hypoglycaemia induced by the dose adjustments, over an extended period. The results showed that differences of mean glucose produced between the three sets of rules were not clinically significant. The most distressing finding of this study was the high incidence of hypoglycaemia for all three algorithms. The Chanock algorithms rated poorly as a huge number of dose adjustments were recommended and the greatest incidence of hypoglycaemia occurred; this judgement was perhaps unfair as the algorithms were used outside their intended domain, which is pump therapy. It can be concluded that the Chanock algorithms are not appropriate for decision support for people who use conventional insulin replacement therapy.

The most successful algorithms, with the above definition of success, were the Skyler algorithms and these deserve to be examined more closely. These algorithms have now passed into the region of acceptable and safe principles of diabetes therapy and are by far the most commonly cited example of an insulin adjustment program. The Skyler algorithms for adjustment of the basal prandial regimen are listed in tables 4.3 to 4.5. The algorithms use milligrams per decilitre (mg/dl) as the unit of blood glucose; to convert to millimoles per litre (mmol/l or mM) the figures may be divided by 18.

Basically, the algorithms use the premises that the fasting blood glucose reflects the adequacy of the long acting insulin dose, whilst the adequacy of each pre-prandial, short acting insulin dose is reflected in the blood glucose measurements taken two hours post-prandially or immediately prior to the next meal (or prior to bedtime for evening meal doses).

If fasting blood glucose > 130 mg/dl for two days increase long acting dose by 1-2 units If fasting blood glucose < 60 mg/dl or if hypos occur overnight decrease long acting dose by 1-2 units

Table 4.3 Existing rules for adjusting long acting dose (Skyler et al 1981)

Points to note about these algorithms are their dependence on timed measurements and the implicit assumptions about regularity of diet, exercise and health. In particular note the assumption that meals will be spaced far enough apart so that the blood glucose should return to a target baseline. It is suggested that only one insulin dose should be changed at a time, especially to counteract hypoglycaemia. Because of the use of an absolute post-prandial blood glucose target, rather than a variable baseline, a short acting dose could be increased even when it has produced a reduction in absolute blood glucose; this would be disastrous if the pre-prandial blood glucose before the dose in question was low. For example: the glucose before lunch may be 14 mmol/l and then may be 15.5 mmol/l two hours after lunch. The lunch time dose of short acting insulin is almost certainly too high but, according to the rules, it would be increased. This is a problem with the sole use of absolute target blood glucose levels during the day. If the pre-lunch blood glucose was 5 mmol/l the next day, an increased short acting dose would be very likely to cause severe hypoglycaemia.

The rules for each of the pre-prandial doses (table 4.4) are identical in format and glucose target for each meal, which neglects circadian variation in blood glucose response, although it does show a pattern which may easily be converted to a generalised basic computer algorithm. Dose adjustments are not closely related to actual glycaemia, although the text includes a suggestion of an alteration of 1-2 units of short acting insulin for each 30-50 mg/dl (1.5-3 mM) above the target.

If blood glucose 2 hours after breakfast > 150 mg/dl OR if blood glucose before lunch > 130 mg/dl for two days increase morning short acting dose by 1-2 units

If blood glucose after breakfast or before lunch < 60 mg/dl OR if a hypo occurs between breakfast and lunch decrease morning short acting insulin by 1-2 units

If blood glucose 2 hours after breakfast > 150 mg/dl BUT blood glucose before lunch < 105 mg/dl consult your doctor or clinician

If blood glucose 2 hours after lunch > 150 mg/dl OR if blood glucose before supper > 130 mg/dl for two days increase pre-lunch short acting dose by 1-2 units

If blood glucose after lunch or before supper < 60 mg/dl OR if a hypo occurs between lunch and supper decrease pre-lunch short acting insulin by 1-2 units

If blood glucose 2 hours after lunch > 150 mg/dl consistently BUT blood glucose before supper < 105 mg/dl consult your doctor or clinician

If blood glucose 2 hours after supper > 150 mg/dl OR if blood glucose before bedtime > 130 mg/dl for two days increase pre-supper short acting dose by 1-2 units

If blood glucose after supper or before bedtime < 60 mg/dl OR if a hypo occurs between supper and bedtime decrease pre-supper short acting insulin by 1-2 units

If blood glucose 2 hours after supper > 150 mg/dl consistently BUT blood glucose before bedtime < 105 mg/dl consult your doctor or clinician

Table 4.4 Existing rules for adjusting pre-prandial short acting doses (Skyler et al 1981)

Table 4.5 outlines the provisions suggested by Skyler for supplementary (extra from standard) short acting insulin. Supplementary short acting insulin is advised when pre-prandial blood glucose tests are high but is not suggested to counteract extra food, exercise or illness.

If blood glucose before breakfast or before supper > 140 mg/dl
take extra 1-2 units short acting insulin

If blood glucose before breakfast or before supper > 200 mg/dl
take extra 2-4 units short acting insulin

Table 4.5 Supplemental insulin doses

General guide-lines for diet are given to accompany the algorithms, especially to counteract the risk of hypoglycaemia due to exercise. It is suggested that extra carbohydrate-based snacks should be used to compensate for exercise rather than a reduction in insulin dose (a negative supplement in effect); 10-15 grams of carbohydrate is suggested to cover 30 to 45 minutes of

activity. Consideration of the patient's current weight is very simply treated. It is recommended that insulin dose adjustments should be limited to 1 unit for patients under 40 kg in weight. Patients over 40 kg in weight (i.e. the vast majority of adults) have to choose between 1 or 2 units. Note that the dose adjustments are absolute and take no account of the current dosage or sensitivity of patients to insulin. Overweight patients, or those who are highly insensitive to insulin require higher than average insulin doses and the small increments suggested would not be sufficient to counteract rising glucose levels, especially if blood glucose measurement is not carried out daily.

The success of intensive dose adjustment algorithms, such as the Skyler algorithms, depends on regular blood glucose monitoring, careful adjustment of insulin dosage and patience. Careful documentation is essential as it is often difficult for a doctor or clinician to help a patient who is adjusting insulin without clear details of test results, insulin doses taken and other factors.

The Skyler algorithms have formed the theoretical basis of attempts at a patient oriented insulin dosage computer (Albisser et al 1985, Pernick and Rodbard 1986, Gomez-Aguilera et al 1987 - see chapter 3) However, there are many problems not addressed by these algorithms; computers potentially offer far more facilities and more flexibility was required as well as attention to making the use of the computer easier and more acceptable to patients.

There were, however, encouraging results of computer systems using simple algorithms. Therefore, heuristic algorithms based on clinical practice, but adapted for more regular home use, were used as a starting point for the new POIRO system. General guidelines were provided by knowledge elicitation, based around the clinical practice outlined in the next subsection. The algorithms separate into methods of assessing blood glucose control and the use of the assessments in dose adjustment and the following subsections are also divided in this way.

General Guide-lines for the Basal Prandial Insulin Regimen

The algorithms described below, which were conceived and developed for this project, refer to adjustment of the basal prandial insulin regimen. Holman and Turner (1987) described the initialisation of basal prandial therapy and adjustment guide-lines (tables 4.6 to 4.9) which form the foundation of these algorithms. The first of these tables contains general guidelines without specific suggestions on amounts of insulin changes.

Diet and Weight
If overweight the dietician will recommend a slimming diet.
Aim to maintain ideal weight.
Take regular meals at the same times every day.

Background insulin supply
Ultralente insulin provides the background insulin supply your body needs. It should be taken every evening, irrespective of nightwork, missed meals or illness.

Insulin for Meals
Your doses of soluble (short acting) insulin are matched to your meals and injections should be taken 30 minutes before them. Soluble insulin acts for approximately 6 hours. You will need to take a snack 3 hours after a main meal and its injection to avoid hypo reactions. Adjustment of your soluble doses allows your treatment to be flexible. If you know you will be taking unusual amounts of exercise or an unusually small meal reduce the preceding dose of soluble insulin. If you will be eating a particularly large meal, take extra soluble insulin beforehand.

Table 4.6 General Guide-lines for patients who are following the basal prandial insulin regimen.

The second table (table 4.7) suggests an ideal target range for pre-prandial blood glucose and suggests a one-off increase in short acting insulin if test results are persistently high. This is obviously crude and inadequate for accurate optimisation. As for the general guidelines, it is not explicitly stated how high glucose tests may be, nor for exactly how many days they may remain high, before an adjustment should be carried out. These figures had to be elicited from an expert as a rule of thumb, they may be different for different people.

If you are measuring your blood sugar, you should aim for levels between 4 and 7 mmol/l before the main meals and before bed. This may be achieved by adjusting your insulin doses and diet. Aim for an overall pattern of good control. Don't worry about occasional stray results. For example if your test before lunch has been over 10 mmol/l on several days you should increase your morning soluble insulin by 4 units and check that the blood test before lunch comes into the correct range.

Table 4.7 Blood Glucose measurements

An improvement on the Skyler algorithms are the suggestions for short term insulin adjustment in cases of illness, the suggestions of table 4.8 are based on pre-prandial blood glucose tests and are thus dependent on accurate, regular monitoring. It is accepted that insulin requirements increase considerably with even quite minor illnesses such as a cold; more serious infections and viruses may cause severe hyperglycaemia and ketosis without proper care. Supplementary insulin may thus be automatically added in times of illness even if a blood glucose test is not carried out. This is one rule of thumb, extracted by knowledge elicitation, which is useful for dealing with missing data.

If you are unwell, measure your blood sugar or do a urine test. If these are high, increase your next dose of soluble insulin. With experience you will find what extra dose of insulin is required. Many diabetics find that 4 extra units are required for a blood sugar level of 12 mmol/l before meals and 8 extra units for a blood sugar level of 16 mmol/l. Even if you are unable to eat you should continue to take your ultralente insulin. If you are unwell and your blood sugar or urine tests are persistently high and you feel thirsty you should consult your doctor.

Table 4.8 Illness

Ultralente insulin is essential for background insulin needs and must not be stopped even during ill health; however, the situation with regard to extra ultralente insulin during ill health is not so clear. The dangers of possible prolonged hypoglycaemia associated with excessive ultralente insulin make it imperative that the ultralente dose is only adjusted with respect to fasting blood glucose results and overnight hypoglycaemia. The guidelines for hypoglycaemia (table 4.9) do not suggest dose reduction in order to avoid a repetition of the hypoglycaemia episode on successive days; in fact, no explicit advice is given on how to reduce insulin in response to low blood glucose test results (i.e. those below 4 mmol/l). Presumably patients' sense of self-

preservation is assumed to prompt a dose reduction, whereas a push is required to encourage dose increases.

Always carry glucose tablets with you. If you have a hypo, bite two tablets and swallow them. Eat an additional two tablets if you remain hypo. Never drive a car or operate machinery whilst you might be hypo.

Table 4.9 Hypoglycaemia

All patients who are started on the basal prandial regimen should be aware of these guidelines and should aim to follow them; most people find that problems occur in adjustment of the insulin - the fine-tuning process required for optimisation of control. One prolonged hypoglycaemic reaction is often enough to make patients nervous about further adjustments. The following sections describe further knowledge elicited from experts and the literature which formed the actual work carried out to improve on the Skyler algorithms and to build on the guidelines of tables 4.6 to 4.9.

IMPLEMENTATION - STAGE TWO

The algorithms for assessing the effectiveness of long acting and short acting insulin are totally separate and are treated in different sections below. However, some of the concepts introduced in this work are common throughout and are introduced first. In particular, the methods used to allow for missing data are novel, and the use of glucose variation from calculated target values (called offset glucose values, or just offsets) are totally new to the field and have been introduced in this work. Provided meal times and insulin doses are entered, it is possible to use default reasoning to estimate glucose values at the different times of day, provided that glucose results are entered often enough, in order to provide information on the suitability of advice.

Calculation of pre-prandial blood glucose moving averages and moving standard deviations are central to the use of defaults in order to allow for missing glucose values. Blood glucose values are initially entered with an uncertain time of day. Once a meal is entered the blood glucose is labelled with the appropriate time of day. A record is kept of the total number of pre-prandial

blood glucose determinations for each of the four times of day (n in equations E4.2 and E4.3). The previous most recently entered blood glucose for the time of day is found and the number of days since this was recorded is calculated; this time difference in days (dd in the same equations) is used to bias the moving average to the newly entered figure. Equation E4.2 updates the moving average pre-prandial blood glucose and equation E4.3 likewise updates the moving average variance which is subsequently used to calculate the standard deviation.

$$\text{new average} = (1/n + dd/30) * \text{new value} + ((n-1)/n - dd/30) * \text{previous average} \quad \text{(E4.2)}$$

$$\text{new variance} = (1/n + dd/30) * (\text{new value} - \text{new mean})^2 + ((n-1)/n - dd/30) * \text{previous variance} \quad \text{(E4.3)}$$

From observation of the relative weights of glucose measurements it appears that the number 30 in the denominator of equation E4.2 does not place an intuitively high enough bias towards new readings. A value of 10 in the denominator would seem to provide a more intuitively correct bias. This has been demonstrated in reruns of patient data. Note that as n gets large the weighting of the most recent reading tends to a limit of 3.3% with a figure of 1/30 but would tend to 10% with a figure of 1/10. With the figure of 10 however, if no reading is entered for 10 days then the weight of a new value would be 1; i.e. all readings older than 10 days would be ignored. In order to comply with the rule of thumb that 30 days of readings have some relevance the figure of 30 is used. More elaborate systems of producing a weighted average are probably unnecessary at this stage but the system does require an intuitively correct feel to the bias.

Clinical safety limits for blood glucose have to be observed; this is carried out in the following way. When a glucose value is entered it is checked against pre-set extreme limits which the

physician has deemed to be dangerous for the patient. If these limits have been exceeded a warning is immediately displayed as well as a request to repeat the reading one hour later. Limits are originally set at 2 mmol/l and 20 mmol/l. If two successive tests fall outside of the pre-set range a message is displayed to consult a physician for advice.

The effect of each insulin dose, whether long acting or short acting, is reflected in the test results of a particular time of day. For short acting doses, the values following the next meal reflect the effectiveness of the dose taken. For long acting doses the only value used to reflect the effectiveness is the next day's fasting glucose. Whichever glucose is used, the principle of insulin adjustment depends on recording the difference, the glucose offset, between the expected (or ideal) blood glucose and the value actually recorded. The method of calculating an expected value varies for different times of day and types of insulin. The procedures for adjustment of the types of insulin are detailed below.

Assessment of the Long Acting Dose by Fasting Glucose Determinations

Long acting insulin is traditionally increased when the fasting glucose is above a fixed target set by the physician. This takes no account of the variability of fasting glucose levels previously recorded and therefore takes no account of the risk of a hypoglycaemic reaction. One suggestion which has been put forward for incremental optimisation is to set a high target fasting blood glucose at first and to gradually reduce the target at clinic appointments until either complete normoglycaemia is achieved or else a limit is attained where any further reduction of the target results in regular night-time hypoglycaemia (Albisser et al 1985).

However, this method is inflexible and not specific to the individual patient concerned; it also requires a high level of physician involvement and a prearranged plan for the target decrements. A more appropriate method of setting a target fasting blood glucose would take variability and mean of the levels already recorded and use them to calculate a target which would give an acceptable risk of hypoglycaemia. This is accomplished in POIRO by a newly developed calculation involving the moving average fasting blood glucose and standard deviation.

Assume the threshold at which patients experience debilitating hypoglycaemia is 2.5 mmol/l. Assume that patients accept a 5% risk of hypoglycaemia. In principle, the distribution of fasting blood glucose measurements may be used to calculate the probability of a blood glucose less than 2.5 mmol/l occurring, if the probability is less than 0.05 then the dose may be safely increased, otherwise it may not. If a normal distribution is assumed for the fasting blood glucose (fbg) then the target blood glucose is set by equation E4.4.

$$\text{target fbg} - 2 \text{ standard deviations} = 2.5 \text{ mmol/l.} \qquad \text{(E4.4)}$$

The standard deviation is calculated from the current moving standard deviation by a ratio between the current moving average and the target. For small numbers of fasting blood glucose measurements, e.g. in the initialisation stage, the coefficient of variation may well be larger than 50%, in this case a maximum target fbg is used, this was set to 9 mmol/l.

Observation of the actual distribution of blood glucose readings in patient trials led to the assumption that the normal distribution would be a reasonable approximation of the distribution of fasting glucose values (fig 4.13). Further analysis by the author, in 11 other subjectsof clinical trials, of higher moments of the mean (skewness and kurtosis, equations E4.5 and E4.6, σ = standard deviation) has indicated that a more appropriate empirical distribution of fasting blood glucose may be the Weibull distribution or the generalised lambda distribution (Dudewicz and Mishra 1988 p228). Problems with fitting data to the normal assumption include the physical lower limit on blood glucose set by the hypoglycaemic threshold of around 1-2 mmol/l for many patients and the lack of accuracy of blood glucose testing strips for both low and high blood glucose tests (there is, in effect, no upper limit on blood glucose).

$$\text{skewness} = \frac{E(X - E(X))^3}{\sigma^3} \qquad \text{(E4.5)}$$

$$\text{kurtosis} = \frac{E(X - E(X))^4}{\sigma^4} \qquad \text{(E4.6)}$$

Further research in this area should centre on the possibility of calculating an inverse distribution function for the actual values recorded. This is possible for a wide range of mean, variance, skewness and kurtosis; it is usually easiest to calculate a distribution with a generalised lambda distribution approximation (Ramberg et al 1979). For simplicity, and due to lack of sufficient evidence to assume otherwise, the normal distribution is used in the present algorithms.

The offset glucose is thus calculated by subtraction of the actual fasting blood glucose from the target fasting blood glucose. This value is recorded and is used to update the moving average offset blood glucose.

Assessing the Effectiveness of Short Acting Pre-prandial Insulin Doses

When meals are taken the blood glucose rises to a peak before the short acting insulin formulations currently available begin to have an effect. The timing of injections before meals affects the duration of the glucose perturbation and the peak blood glucose of the post-prandial blood glucose curve (fig 4.14); this has been demonstrated by Kraegen et al (1981) who showed that the optimum delay between soluble insulin injections and meals is approximately thirty minutes for most individuals. It is assumed that patients follow a relatively constant routine when injecting, although no assumptions are made about the delay between injections and meals. It is mandatory, in this system, that the meal about to be taken is recorded before insulin dose advice is requested. Patients are therefore instructed to record their intended meal size when requesting insulin advice, even if they are not actually eating for half an hour.

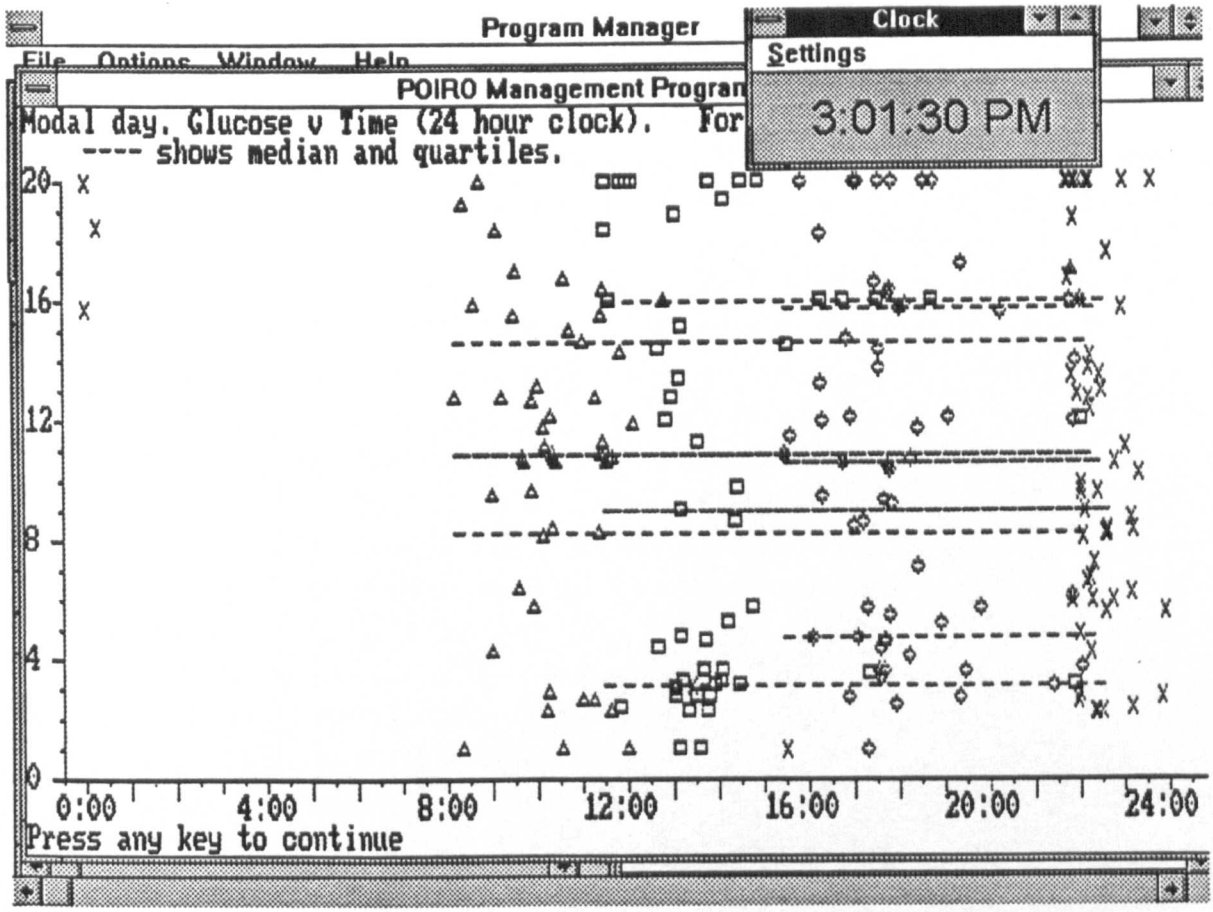

Fig 4.13 An example of a set of blood glucose values over a four week period for a single patient. Exhibits a good example of day-to-day variation in glucose levels and meal timing. The symbols represent different meal times. Δ = am (breakfast), • = md (lunch), ◊ =pm (evening meal), X = snacks (mostly before bed).

Note the distribution of the number of blood glucose values around a mean for each of the meals. Take breakfast for example (the symbol Δ denotes a pre-breakfast blood glucose reading). The mean is approximately 6 mmol/l for this patient with most readings close to the mean and a small number of readings forming the tails on either side (above and below) this mean. A more mathematical analysis of actual blood glucose results is explained in the text.

It is not feasible, in most circumstances, for patients to time their post-prandial blood glucose measurements at exactly two hours after a meal, as required by the Skyler algorithms. It is probably better to encourage tests at the most convenient time for patients, which may vary from day-to-day. In order to allow blood glucose measurements to be entered at any post-prandial point the first requirement was to represent the expected ideal blood glucose response to meals.

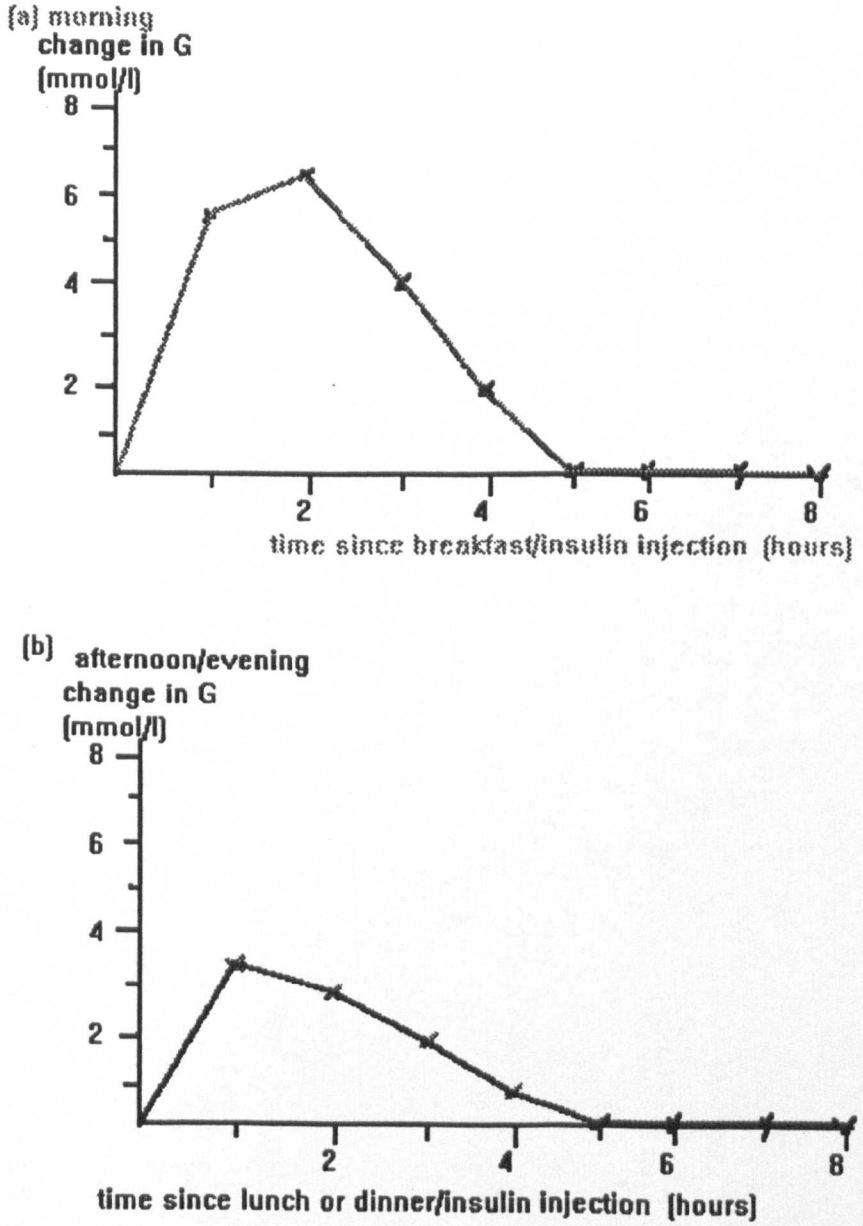

Fig 4.14 Meal reference curves: (a) Breakfast, (b) Lunch/Dinner.

The curve displayed in fig 4.14 shows the mean of nine insulin dependent diabetic patients' blood glucose levels over six hours after breakfast (a) and the evening meal (b). These curves are used as an empirical "ideal" reference in order to estimate blood glucose levels after meals given the glucose level before the meal. This estimate is then compared to the value entered and assesses the effectiveness of the preceding short acting insulin dose.

In order to justify the use of this system it is assumed that the blood glucose determinations during any day are related to the fasting glucose on that day which provides a baseline level. The fasting glucose has been shown to remain a relatively stable entity in the absence of food, illness or unusual exercise and should be especially so with effective long acting (ultralente) insulin dosage, as employed in the basal prandial therapy regimen. The pre-prandial, short acting doses should aim to counteract the post-prandial rise in blood glucose and to regain the pre-prandial level before the following meal time or bedtime in the case of the evening meal dose. The system of relating to an ideal curve thus makes no assumptions about the baseline level, it isolates each insulin dose for individual assessment. The system is an improvement on the Skyler algorithms, which use absolute target blood glucose levels throughout the day, as the effect of multiple dose adjustments should not induce hypos and the system is not limited to one adjustment per day.

In addition to these assumptions, the determination of trends through the day, i.e. circadian variations, is central to optimisation of the pre-prandial short acting insulin doses. For this reason the response of the blood glucose after each meal and insulin dose is assessed by an offset glucose value. This is the glucose actually measured less the expected blood glucose at that time. For example if the pre-breakfast (fasting) blood glucose was 9 mmol/l and a value of 14 mmol/l is recorded 3 hours later, the expected value at that time would be 9 + 4 (obtained from the curve in fig 4.12(a)), i.e. 13 mmol/l; therefore, an offset blood glucose of 1 mmol/l is recorded for that day and is used to update the mean offset for the breakfast insulin dose.

A moving average glucose offset is calculated after each blood glucose event is entered; the two most recent glucose offsets are also retained for each time of day. When the appropriate insulin dose is adjusted (see next subsection) the moving average and these two offsets are reset to zero.

Insulin dose adjustments are calculated with respect to glucose offsets and are related to the current default doses and insulin sensitivity. Dose adjustments should not exceed a fixed percentage of the current dose for ethical and safety reasons. The maximum dose increase should be more restrained than the maximum dose reduction as the short term effects are more acute with dose increases which may lead to severe hypoglycaemia than for dose reductions which are unlikely to cause immediate ketosis (the opposite extreme in blood glucose level).

The procedure carried out when a blood glucose test is entered is as follows. When a glucose test result is entered, the system checks previous event entries for the last meal entered. If this was within 10 minutes it is assumed that the reading is a pre-meal reading for the meal and it is labelled as such in its *time of day* slot; at the same time, the routine which updates the pre-prandial blood glucose moving average is called, and the moving average and standard deviation are updated with the new value. The search is then continued back to the next most recent meal.

If the time since the previous meal is more than 10 minutes, but less than 8 hours, the system checks the change in glucose from the previous meal; this is termed the offset. In order to do this an expected blood glucose is calculated and the recorded value is compared to it to give an offset. If an actual blood glucose value was entered at the previous meal it is used as a base, otherwise the moving average value for the meal is used. Equation E4.7 calculates the expected glucose value. Equation E4.8 calculates the offset. The expected offset in equation E4.7 is derived by a simple linear approximation from the curves for meal time excursions given in fig 4.14.

$$\text{expected value} = \text{previous value} + \text{expected offset} \quad \text{(E4.7)}$$

$$\text{actual offset} = \text{actual value} - \text{expected value} \quad \text{(E4.8)}$$

Checks are then carried out on the exercise, health and insulin entered with the previous meal, and for hypos since the meal. If a hypo was recorded then both the glucose value and the offset are ignored and the insulin dose is altered according to rules for hypos. The reason for discarding the glucose value is that hypos are breakdowns in normal routine and the snack taken to counteract the hypo may have affected the glucose reading.

If any of the other factors (exercise, health), are NOT normal or the insulin dose taken is not the dose advised then the moving average offset is not updated but the offset is recorded.

When either the moving offset is outside pre-set limits OR two successive offsets are outside slightly less tight limits (2 mmol/l), the dose may be changed. The dose is changed when it is next requested; more details are given in the next subsection.

The POIRO Algorithms for Insulin Dose Adjustment

Fig 4.15 shows the screen obtained by selection of "INSULIN" from the main menu. The screen is used to obtain an advised insulin dose, and to enter the dose taken should this be different. The explanation screens generated by pressing the "Explain" option are also shown. These are generated by a mix of canned text and the text of the original event screens. They are not sophisticated explanations in the true sense of expert system explanations but provide useful justification of dose adjustments for subjects. The explanation screens also act as confirmation that the patient entered correct information; if any information is incorrect it may be changed after quitting from the insulin screen; the correct insulin dose may subsequently be obtained. The procedures used to produce the advised dose are now described.

Once the effectiveness of each insulin dose is assessed, algorithms for adjustment of inadequate doses may be used. The glucose assessment offsets described above are used to calculate insulin

adjustments, rather than single glucose values as used in previous algorithms. The novel use of a dose adjustment curve, described below, is useful as it shows in pictorial form how adjustment depends on the offsets calculated using the algorithms. The method of calculation is identical whether the insulin is long acting or short acting, however, such parameters as sensitivity may differ for different insulin types.

In principle, it should be possible to calculate insulin dose adjustments by a simple equation such as eq. E4.9; here the original dose D_0 is incremented by a constant S multiplied by the average glucose offset $\mu(g)$ to give a new dose D_1; this is illustrated in fig 4.16(a).

$$D_1 = D_0 + \mu(g).\, S \qquad \text{(E4.9)}$$

The constant S is the sensitivity of the patient to the type of insulin and varies considerably between individuals. For the moment, assume S = 1.

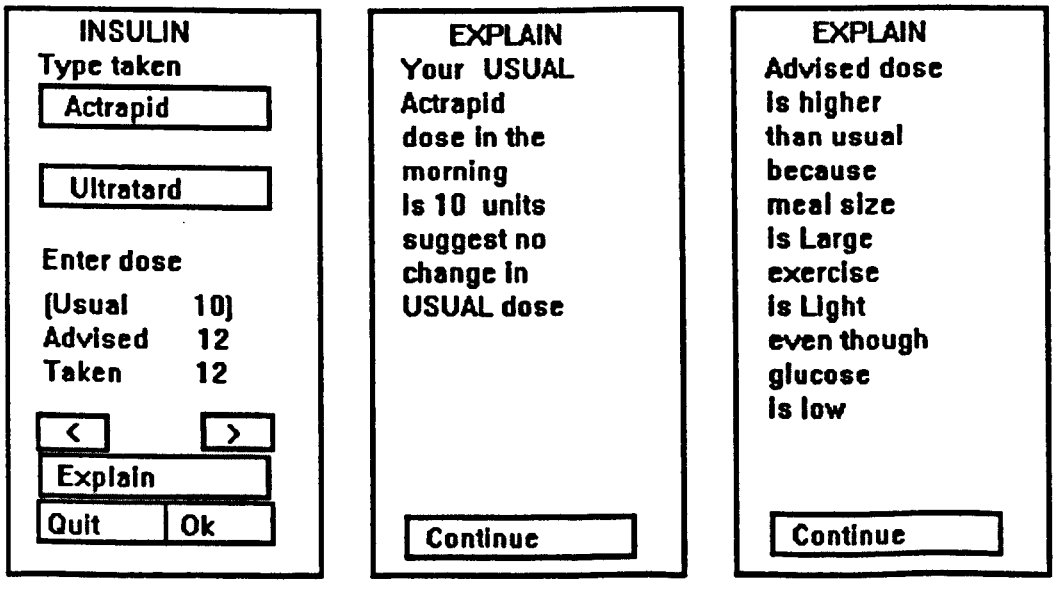

Fig 4.15. The INSULIN screen and example explanation screens for an Actrapid dose taken in the morning before a large breakfast when expected exercise is light. The low blood glucose is taken into account but is outweighed by the other factors of meal size and exercise level..

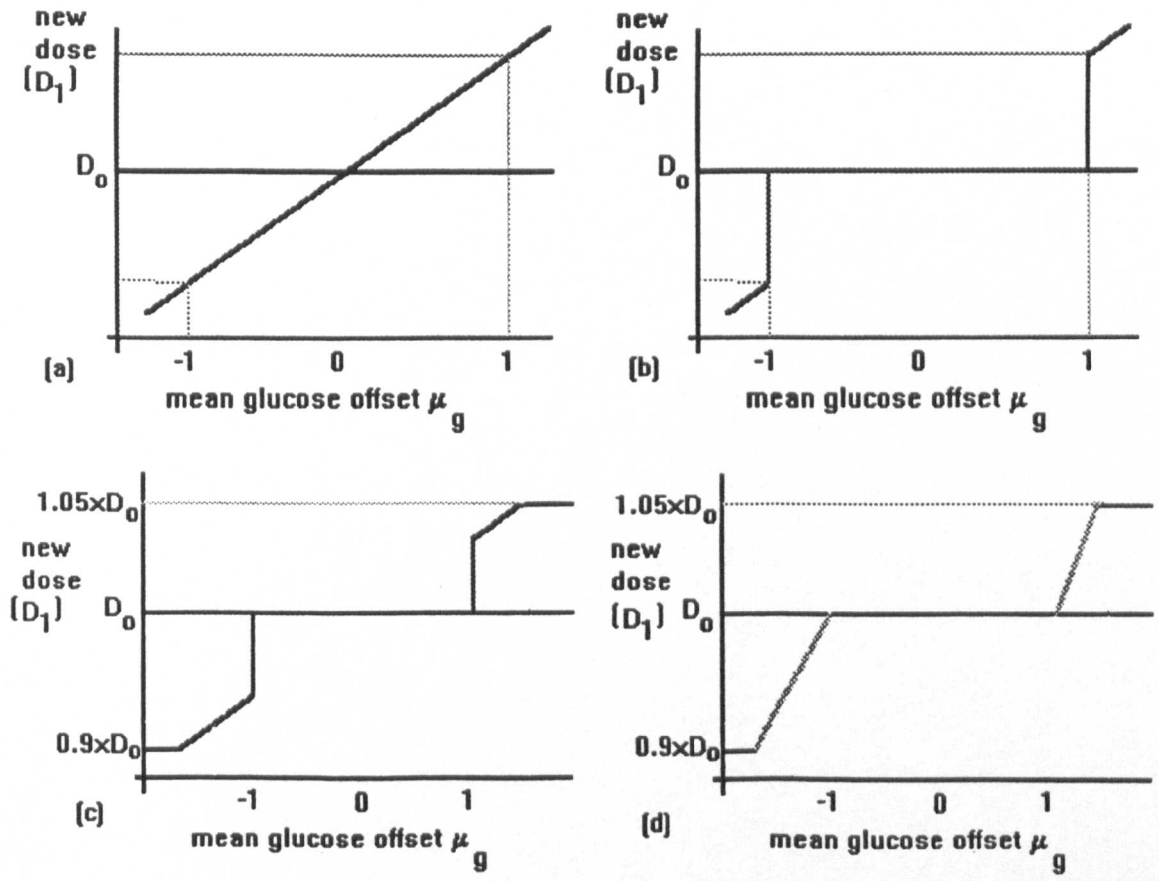

Fig 4.16 Relationship between glucose offset μ(g) *and dose change (a) basic line, (b) limits of range, (c) limits of dose change added (implementation curve), (d) possible improvement by translation of dose changes.*

Although a target blood glucose value is defined, it is perfectly acceptable for the glucose to fall within a range of 2 mmol/l around this target (on average). Therefore the dose is not changed if the average offset is within 1 mmol/l of the target (fig 4.16(b)).

Safety considerations dictated that any one dose increase must not exceed 5 % of the current dose (except cases where 5% of the current dose is less than one unit). Dose reductions are limited to 10% (although there is similarly a 1 unit minimum reduction). Incorporation of these limits leads to the characteristic curve shown in fig 4.16 (c). Points to note about fig 4.16(c) are the slope of the curve and the discontinuities (jumps) at offsets of 1 and -1 mmol/l. The piece-wise equation for this curve is given in equation E4.10, where min and max have the usual meanings of minimum and maximum value of the expressions within the brackets. It was the equation used in the POIRO algorithms.

$$D_1 = \begin{cases} D_0 & |\mu(g)| \le 1 \\ D_0 + \min(\,1, \max(\,0.05 \times D_0\,, \mu(g) \times S\,)\,) & \mu(g) \ge 1 \\ D_0 - \min(\,1, \max(\,0.1 \times D_0\,, |\mu(g)| \times S\,)\,) & \mu(g) \le -1 \end{cases} \qquad \text{(E4.10)}$$

Note that if the original dose D_0 is less than 30 units, the increase in dose will always be limited to 1 unit. Similarly for dose reductions the decrease is limited to 1 unit whilst the current dose is less than 15 units. Provided that a dose change has to be made when the moving average offset is more than 1 mmol/l the dose change of short acting insulin will be limited to 1 unit in many normal weight cases. The expected short acting dose for normal weight, average height man is approximately 40 units (Holman and Turner 1985) which is divided amongst two or three pre-prandial doses.

For general insulin sensitivity S the dose increase will be limited to 5 % if S is greater in magnitude than D/20 as the minimum value of $\mu(g)$ for a change to be advised is 1. Similarly, the decrease will be limited to 1 unit if S has a numerical value less than D/10. Further studies are required to estimate the effect of changing the percentage limits on dose changes.

The curve shown in fig 4.16 (d) is an attempt at "smoothing" the dose adjustment function, many other variations are possible and an interesting area of further study may be to compare the effectiveness of each of these curves.

As stated earlier, the moving average offset is not updated unless all the factors which affected the corresponding insulin dose were normal and the advised dose was taken. However, the actual offset is recorded, provided there were no hypos in the intermittent period. The insulin dose is also altered if two successive offsets for the particular time of day are greater than 2 mmol/l or less than -2 mmol/l. In this case the offset used in equation E4.10 is the average of the two offsets.

Adjustments due to Hypoglycaemia.

If hypoglycaemic reactions are recorded, previous insulin doses and meal times are checked in order to ascertain which insulin dose was responsible. If this analysis is successful, the insulin dose is reduced by 10% immediately and dose offsets are reset to zero. A problem with this procedure is the possibility of recording hypos more than once. The dose of insulin would be reduced twice.

A better procedure for future use would be to record the hypo with the time of day of the insulin dose to be changed. The hypo would then only alter the appropriate insulin dose when the dose was next requested. A further refinement would be to check for discrepancies between hypoglycaemia and high positive offsets. Although, in most cases the correct explanation would be either that the positive offset was due to excessive snacking or that it was due to the so called Somogyi effect; i.e. hypoglycaemia due to excessive insulin can lead to excessive (rebound) hyperglycaemia. The effect is most often found with excess long or intermediate acting insulin taken to cover night-time requirements. In other words, hypoglycaemia is always given priority and doses are always reduced as is the case with existing algorithms.

Supplementary Insulin Doses

Once algorithms for adjustment and optimisation of the standard insulin doses were developed, further refinements were carried out to allow for non-standard meals, exercise and health. These refinements were based on an encapsulation of the usual practice of physicians at the featured clinics in Oxford. The use of supplementary insulin adjustments for such wide ranging factors is new to this system; it requires much research and refinement of the physician level software so that the algorithms may be tailored to individual requirements.

Supplementary insulin doses are advised when any of the events related to the short acting insulin dose are not normal. The system proposed here is a simple relative multiplication factor system. Table 4.10 lists the factors and the multiplicative constants to be used to calculate the short acting insulin dose.

Table 4.10 Supplementary insulin calculation multipliers

FACTOR	OPTION	MULTIPLIER
Meal Size	Nothing	0
	Light	0.6
	Normal	1.0
	Large	1.5
Exercise	None	1.2
	Minimal	1.1
	Normal	1.0
	Heavy	0.75
Health	Well	1.0
	Unwell	1.2
	Very Ill	1.5

Default (standard) insulin doses are taken when no information is available whatsoever. By default, it is assumed that all factors not entered are "Normal". In all cases where an item such as exercise is missing, the insulin dose multiplier for the missing item is set to 1.0.

Note that the multiplier for a meal size of "nothing" is zero. This over-rides all other multipliers except high glucose values. In cases of high glucose values, the glucose-related

insulin dose multiplier is used to calculate a supplementary dose which would be given if all other factors had their default values, i.e. 1.0. In cases of missing or low glucose values in conjunction with a meal size of "nothing", the dose of short acting insulin is set to zero.

As outlined below, these multipliers may be customised to individual patients. For instance patients who are extremely sensitive to prevailing pre-prandial blood glucose may require much higher multipliers for the blood glucose section; this data is not directly under the patients' control to alter, but is the responsibility of the prescribing physician.

Non-compliance

Non-compliant patients do not follow advised doses of insulin. Non-compliance has been seen as a major problem in diabetes therapy (Bloom and Hart 1980) and has been blamed as a cause of so-called brittle diabetes (O'Hare 1987). Where psychological reasons for non-compliance are present then there is little that can be done until the psychological reasons are investigated and treated. However, non-compliance may be due to patients belief that they know that a different dose is required. Previous systems have failed to acknowledge non-compliance of this type and even when acknowledged it has never previously been utilised.

Rules for doses taken that are different from those advised check whether the resultant offset was within the target range. If not, then if the offset is positive despite more insulin than advised or the offset is negative despite less insulin than advised, then the dose taken was better than the dose advised. The dose taken is subsequently used as a base for future days.

Use of the Notebook

The notebook option is available at any time via the *INFORM ME* option; it is also provoked automatically by certain events within the normal data entry sequence: hypos, unusual blood glucose values and non-compliant insulin doses are all questioned for a reason. Unusual blood glucose values are defined as those which are not within two standard deviations of the moving

average blood glucose value for the time of day. Another situation where the notebook may be useful would be for ill health events.

The notebook explanations entered by patients are a useful research facility as they may later be categorised into a menu system if any perceptible pattern emerges. For example, it may be that hypos may be related primarily to just the four overall categories of unexpected exercise, illness, inadequate diet or changes in the insulin dose; these options may be offered as a sub-option after a hypo event is recorded, i.e. by a menu showing Exercise, Illness, Diet or Insulin and may, in turn, trigger rules for adjusting insulin by different amounts. In one of the few previous studies of reasons for hypoglycaemia it was shown that most episodes of hypoglycaemia are due to changes in activity or diet and not to changes in the insulin dose (Swenerton et al 1991).

THE POIRO MANAGEMENT PROGRAM (PMP).

Several parameters need to be set by the physician when new patients begin to use the POIRO system for the first time. In particular, physicians need to decide on the target blood glucose levels, safe limits on insulin dose adjustments and the multipliers for supplementary short acting insulin. Default values for the multipliers and target blood glucose levels are provided. Insulin dose limits may be set to plus or minus 50% of the starting dose or 6 units, whichever is the greater. This should give a reasonable margin for safety whilst still allowing several dose increases

All parameters concerned with the adjustment of insulin doses may also be altered. Especially the offset range before doses may be increased, as depicted in the dose adjustment curves of fig 4.16; this is presently set at 1 mmol/l. The time delays between meals and preceding or succeeding glucose values, the sensitivity to insulin, and the maximum permitted percent increase or decrease of insulin dose may all be given different values although the default values are probably most appropriate for initial trials with the device.

A close relationship between the physician and patient system is an essential factor mentioned in the conclusion of chapter 3. A simple facility for transferral of data from POIRO to the control system was required. Communication programs originally designed for the system were far too complex for use by non-computer oriented physicians. Special routines were developed which are simply activated by the physician connecting the two computers with a simple cable and then pressing the appropriate key on the physician's PC. The routines were limited slightly in speed due to the use of a portable PC for transfer of the data away from normal sites during the clinical trials (see below). With the advent of portable computers with much faster processing power, the transfer of a complete file of two thousand data items is considerably speeded up and should take less than one minute.

The physician managerial program contains many data presentation and summarisation routines. Statistical tables may be generated showing minimum, maximum, median and quartiles of glucose and insulin data. Graphs of insulin doses and glucose test results by time of day may be viewed. Overall glucose control is assessed by a box and whiskers plot; the overall control graph also includes an option to show the daily M-value (Schlichtkrull et al 1965) plotted for any three week period.

Other information of interest includes statistical summaries of glucose in terms of the moments about the mean: i.e. the mean, standard deviation, skewness and kurtosis. A graph showing mean daily blood glucose versus mean daily standard deviation as first suggested by Piwernetz (1990) is included. Glucose data are divided into those recorded with computer advice and those without computer advice and "best fit" straight lines are calculated and plotted for the two sets of data for comparison.

EVALUATION AND VALIDATION

Introduction

Two methods of evaluation and validation have been used for the POIRO system: clinical trial and simulation. Clinical trials were carried out in 1989 and 1990. These trials had common aims to obtain patient feedback about the use of the system and its effectiveness as measured by the parameters of glycaemic control, i.e. pre-prandial blood glucose and long term measurements haemoglobin A_{1c} and fructosamine. The initial trial assessed effectiveness of the algorithms with a fixed target blood glucose whilst the second trial assessed the algorithms with a variable target blood glucose based on the feedback loop of actual mean and standard deviation of blood glucose values recorded.

In order to assess the algorithms theoretically, a metabolic simulation of blood glucose intake and metabolism was written and hooked into the program to simulate a period of one month of insulin dose adjustment. The patient parameters of sensitivity to blood glucose, meal timing and intake, as well as different dose regimens were studied.

CLINICAL TRIALS.

Two formal clinical trials have been successfully completed. The first trial was of controlled, open randomised crossover design; the second trial was of controlled sequential crossover design. Six subjects took part in each of the trials, full details and results of the first trial are given in the next section, followed by a description of the changes made for the second trial and interesting results of the second trial.

Both trials were carried out with the close cooperation of the collaborating establishment in this research, the Diabetes Research Laboratories (DRL), Radcliffe Infirmary, Oxford. Patients were recruited by the Laboratory's diabetic liaison nurse, sister Jill Steemson based on eligibility

criteria set out in table 4.11. After selection, the patients were educated in the use of the POIRO system for about one hour by a clinical collaborator (Liz Pemberton in trial one, Jill Steemson herself in trial two). The clinical collaborator subsequently had to arrange to meet each subject once per week to transfer data from POIRO to the PMP running on a PC. At the start, crossover and end of the trial she also took blood samples for measuring biochemical indices of control. If any subjects were concerned about anything during the trial, medical backup was proved at all times by an expert physician from the DRL and by Sister Steemson (emergency telephone numbers were provided on the "INFORM ME" screen of the hand-held computer as well as on the printed instructions.

The aims of trial one were to determine the effect of the POIRO system on the following factors: pre-prandial blood glucose values recorded by the patients, their overall glycaemic control assessed by mean glycaemia and glycosylated haemoglobin, insulin doses, the number and severity of hypoglycaemic episodes, the subjects' lifestyles and their attitudes towards diabetes and their opinions on the use of computer decision support systems.

Subjects were chosen for the trials on the basis of their control being sub optimal based on historical HbA1c levels in the range 8-10% (normal range 4-7%); full inclusion and exclusion criteria are given in table 4.11.

INCLUSION CRITERIA	
1	History of raised glycosylated haemoglobin - HbA1 > 8%
2	Established user of home blood glucose monitoring
3	Capable of recognising and reacting appropriately to symptoms of hypoglycaemia
4	Current insulin regimen - basal prandial
5	Willing to alter insulin doses on a daily basis
6	Able to make regular contact by telephone
EXCLUSION CRITERIA	
1	History of very high glycosylated haemoglobin - HbA1 > 10%
2	Coexisting steroid therapy
3	Coexisting serious illness
4	Subjects could be excluded at their own or their physicians' request

Table 4.11 Inclusion and Exclusion criteria of subjects involved in clinical trials of the POIRO system

Trial one was carried out during the period October to December 1989. Six subjects (details in table 4.12) were recruited for the study; witnessed informed oral consent was obtained from each person and ethical approval for the trial was given by the Central Oxford Research and Ethics Committee before commencement. The author prepared the six hand-held computers, the portable computer and disks for collecting data and trained the collaborator in the use of the system. Twenty-four hour technical support was also provided by me during both trials. The patients were recruited and educated by the clinical collaborator as mentioned above and 24 hour clinical backup was provided by consultant physicians.

Number	6
Male:Female	4:2
Body Mass Index (kg/m^2)	23.4±2.5
Age (years)	32.0±11.3
Duration of diabetes (years)	12.7±10.9 (range 5-34)
Ultralente dose (U)	30±12
Short acting insulin dose (U)	21±5
HbA1c (%)	9.3±1.3 (range 6.8-10.8)

Table 4.12 Subject characteristics at the start of the first clinical trial

In addition to the criteria in table 4.11, subjects were asked to follow a consistent nature of diet throughout the trial, although changes in size and timing of meals was not discouraged as the device is designed to cope with meal variation. In order to achieve maximum benefit, subjects were advised to carry out daily four point blood glucose profiles. The Exactech blood glucose meter was used by all subjects in order to achieve conformity and accuracy of test results.

Trial Protocol

Subjects each received a device pre-programmed with their existing insulin doses for an initial one week "run in" period with the insulin dose advice function disabled; this period was used to collect baseline statistics and to ensure that subjects were able to use the device successfully. Subsequently, three subjects were selected at random to have the insulin dose advice enabled; the other three subjects continued using the device to enter data only. After the end of the first

three week period, a "cross-over" was carried out and the advice was enabled or disabled as required.

Blood samples for analysis were collected at the commencement of the trial and at the completion of each three week period. In addition, questionnaires were issued before and after the trial in order to elicit the subjects' opinions of their diabetic control, their understanding of diabetes and their attitude to the POIRO system.

Results

Five subjects successfully completed the trial, one subject withdrew after a grade two hypoglycaemic reaction whilst receiving advice. Results quoted below are taken from the run-in period and the final week of the two trial periods, "On" applies to the period with advice enabled and "Off" applies to the period with advice disabled. The major quantitative results are the mean pre-prandial blood glucose and the incidence of hypoglycaemia. In addition, the variability of pre-prandial blood glucose, assessed by coefficient of variation (c.v.) is used to compare glycaemic control. Statistics on the other factors, meal sizes, exercise and health are included to give an indication of the amount of variability in lifestyle of the subjects and the difficulties involved in control under normal circumstances. These figures are also useful to detect misunderstandings in the methods of data entry.

The mean pre-prandial glucose levels for each of the four times of day appear in table 4.13. The results are not significantly different between the two periods with and without advice. However, there was a significant reduction in mean blood glucose between the run-in period and the period with the advice function enabled ($p<0.007$). Regularity of monitoring was high for all except bedtime snack tests which were not previously carried out by the majority of subjects. At least three tests were entered per week by all the subjects for the other times of day throughout the trial.

Subject	Breakfast			Lunch			Dinner			Snack		
number	Run-in	On	Off	Run-in	On	Off	Run-in	On	Off	Run-in	On	Off
1	7.49	7.89	7.70	4.85	5.86	4.81	8.54	6.13	6.81	10.50	7.50	6.41
2	6.85	9.04	9.33	8.70	5.20	8.72	9.63	7.80	8.70	7.98	-	7.90
3	11.35	7.56	8.08	12.61	7.30	5.20	10.19	7.02	5.64	12.10	1†	-
4	6.01	7.35	14.23	13.33	13.28	15.56	13.20	7.16	4.60	10.98	8.20	13.18
5	4.44	*	6.12	10.57	*	7.15	12.07	*	11.22	8.80	*	8.58
6	7.64	6.32	6.96	6.80	7.40	5.44	9.93	6.04	4.33	12.30	7.50	10.35

† less than 3 events
- no events recorded
* subject withdrew from study

Table 4.13 Mean pre-prandial blood glucose results. Comparison of run-in period and final weeks with and without advice.

Subjects 1, 3 and 4 received advice for the first three week period, whilst the other three subjects had the advice enabled for the second three week trial period. There was a tendency for subjects in the first group to reduce their pre-prandial blood glucose during the treatment period and to maintain that reduction in the following period. This suggests that standard doses were not optimal at the start of the trial but were optimised during the advice period and concomitantly that the optimal doses were then continued in the second period. The exception to this was subject 4 who exhibited the highest reduction in blood glucose in the advice period but did not keep up the improvement. An examination of insulin doses taken (fig 4.17) reveals that subject 4 did not, in fact, continue with the optimised doses but gradually regressed towards the doses advised prior to the trial. A second possibility why a continuation of improvement is apparent after advice is removed is due to the educational quality of the advice. Subjects expressed increased confidence in self adjustment of insulin doses on the questionnaires issued.

Figure 4.17 shows that the majority of subjects saw changes in their individual insulin doses, this tended to be in a redistribution of the proportions of long and short acting insulin rather

than significant changes in total daily insulin need. Compliance with advised insulin dose was greater than 90% for all subjects in the trial period and was not a great problem for the system.

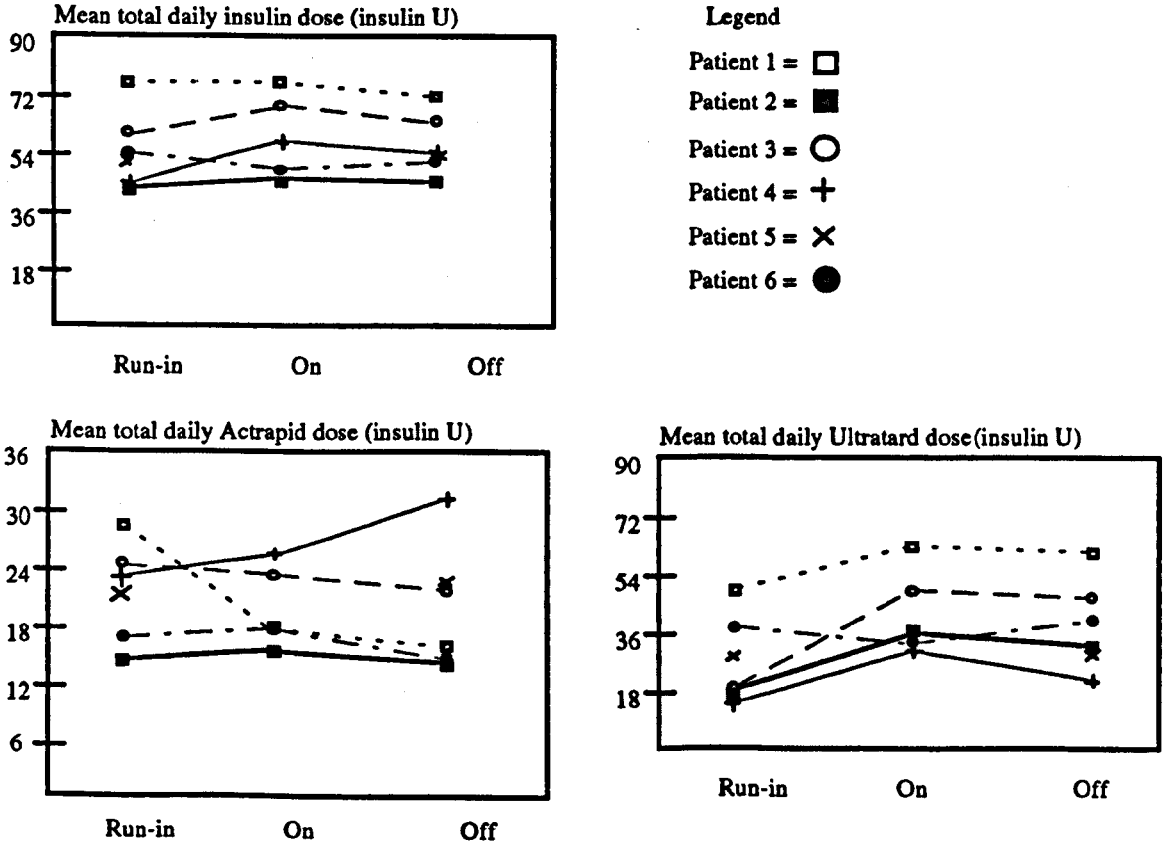

Fig 4.17 Insulin doses taken by each patient during each period of trial one.

Subject	Grade one			Grade two			Grade three		
Number	Run-in	On	Off	Run-in	On	Off	Run-in	On	Off
1	2	2	1	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0
3	1	0	1	0	0	0	0	0	0
4	2	5	4	0	0	0	0	0	0
5	0	*	0	0	*	0	0	*	0
6	0	0	1	0	0	0	1	0	0

* subject withdrew from study

Table 4.14 Incidence of hypoglycaemia, by grade, during each period.

The incidence of hypoglycaemic reactions remained low throughout the trial for all subjects (table 4.14). Subject 4 was again unusual in that the number of grade one hypoglycaemic reactions recorded was higher during the two treatment periods than in the run-in period. The period with advice disabled is particularly perplexing as the subject also exhibited much higher mean blood glucose levels. Analysis of the timing of hypoglycaemic reactions failed to show any trend and it may be that the subject had unusual circumstances. It was recorded in the notebook that she was moving house during the second three week period with advice off, the stress involved in moving house is well known and it is also known that stress disturbs blood glucose levels by similar processes to those involved in ill health. One aspect of the table is the lack of any other than minor hypoglycaemic reactions during the advice period, despite the intensification of insulin therapy.

Subject number	Breakfast						Lunch						Dinner						Snack					
	Run-in		On		Off		Run-in		On		Off		Run-in		On		Off		Run-in		On		Off	
	<	>	<	>	<	>	<	>	<	>	<	>	<	>	<	>	<	>	<	>	<	>	<	>
1	0	0	0	0	0	0	0	33	0	0	0	0	14	0	100	0	14	0	90	0	0	0	100	0
2	0	0	0	0	0	0	83	0	50	0	50	0	0	0	0	0	0	0	0	0	-	-	20	0
3	0	0	0	0	0	0	14	0	0	0	0	0	14	0	0	0	0	0	-	-	-	-	-	-
4	0	0	0	0	0	0	28	0	12	0	12	0	14	14	0	42	16	16	25	11	25	6	25	11
5	0	14	*	*	0	0	28	0	*	*	0	0	0	14	*	*	0	0	50	50	*	*	-	-
6	0	0	0	0	0	0	0	0	25	0	0	0	16	0	0	0	0	0	0	0	-	-	-	-

† less than 3 events
- no events recorded
subject withdrew from study

Table 4.15 Meal results. Percentage of meal sizes less than (<) or more than (>) "Normal" entered

Subject number	Breakfast						Lunch						Dinner						Snack					
	Run-in		On		Off		Run-in		On		Off		Run-in		On		Off		Run-in		On		Off	
	<	>	<	>	<	>	<	>	<	>	<	>	<	>	<	>	<	>	<	>	<	>	<	>
1	0	28	0	0	0	0	0	28	0	0	0	0	56	0	56	0	28	14	40	10	77	0	100	0
2	84	0	100	0	66	0	80	0	100	0	100	0	20	0	0	0	56	0	0	0	-	-	66	0
3	0	0	0	0	40	0	0	0	0	0	0	0	42	0	14	0	0	0	100†	0	100†	0	-	-
4	14	28	0	56	0	42	0	14	28	42	0	14	42	0	70	0	33	16	25	4	54	18	46	14
5	28	0	*	*	16	16	25	0	*	*	0	25	0	20	*	*	0	20	50	50†	*	*	-	-
6	42	0	42	0	0	0	20	0	20	0	0	0	16	16	0	0	0	20	0	0	0	0	0	0

† less than 3 events, - no events recorded, * subject withdrew from study

Table 4.16 Exercise results summary. Percentage of time when exercise less than (<) or more than (>) "Normal" was entered.

The statistics of the percentage of meal sizes, exercise levels and health are presented in tables 4.15 to 4.17. They show relatively little variation in lifestyle between the three treatment periods for most subjects. Where the percentage of meal sizes or exercise levels which are not normal approaches 100% it may indicate a misunderstanding of the method of data entry of these quantities, i.e. the relative scale is in relation to what is normal for the individual not to some hypothetical normal person. For instance, subject 2 regularly entered meal sizes less than normal for lunch and exercise less than normal for breakfast and lunch. Whilst this may have been perfectly correct and explained simply by an illness or holiday from work, such trends may indicate a problem and may be detected by summary statistic screens using the PMP system. This emphasises the importance of the diabetes educator in conjunction with the decision support system. Printed instructions did emphasise the relative scales, although it is unclear how often the instructions were utilised. The importance of correct categorisation of these factors cannot be underestimated as insulin doses are changed from the standard value when the factors entered are not normal and small changes in normal insulin may cause severe hypoglycaemia or hyperglycaemia if the lifestyle changes are only very slight or not carried out.

Subject	Breakfast			Lunch			Dinner			Snack		
number	Run-in	On	Off	Run-in	On	Off	Run-in	On	Off	Run-in	On	Off
1	0	0	100	0	0	100	0	0	86	0	0	100
2	0	0	0	0	100†	0	0	0	0	0	-	0
3	0	0	0	14	0	0	14	0	0	0	0	-
4	0	0	84	0	0	56	0	0	100†	0	0	82
5	28	*	28	40	*	0	40	*	0	0	*	-
6	0	0	0	0	0	0	0	0	0	0	0	0

† less than 3 events
- no events recorded
* subject withdrew from study

Table 4.17 Health results. Percentage of time in each period when ill health was recorded

Apart from minor occasional entries of unwell, subject 1 had a tooth abscess during the advice off period and subject 4 had flu (which may explain some of the earlier observations). Long term changes in overall glycaemia were assessed by blood tests for HbA1c and fructosamine. HbA1c fell in three subjects and rose in one, whilst no comparison could be made in the other two subjects. The results are therefore not significant, although highly encouraging. A total comparison is however available between the run-in period and the advice Off period, this shows improved HbA1c levels in all subjects simply due to the addition of a computer.

Subject	Haemoglobin A_{1c}			Fructosamine		
Number	Run-in	On	Off	Run-in	On	Off
1	9.8	8.7	8.6	400	418	440
2	10.8	10.2	10.6	497	536	646
3	9.2	-	8.9	470	557	459
4	9.1	7.7	8.3	460	459	458
5	6.9	*	6.4	335	*	350
6	9.9	10.1	9.4	450	438	458

- no events recorded
* subject withdrew from study
Table 4.18 Biochemical indices of long term control.

Subjective properties, i.e. qualitative considerations are now discussed. The reliability of the computer and the program itself was high for a piece of previously untried software. Just two problems occurred which were quickly corrected. The first problem was due to a subject who entered a zero for a reading of "LO" on his blood glucose meter. This happens for the Exactech meter for a blood glucose less than about 2 mmol/l. The glucose procedure was then modified to permit values no less than 1.0 to be entered. In addition, to allow for the range of meters two extra buttons for "HI" and "LO" were added to the glucose screen.

The second problem was due to battery failure. Data was lost from the events file whenever the battery failed or there was a software fault such as the one described above. A facility to make sure that data is saved (or in computer terms "flushed") to the disk was included once this problem came to light. Smart card routines were also tested but the limits of speed and data capacity are too great for this to be acceptable to patients in the present state; (there is a delay of approximately 15 seconds for writing to the smart card).

There was a very positive general reaction to POIRO from subjects. The questionnaires, which were devised in collaboration with the consultant physician, and administered by the clinical collaborator, showed evidence that patients who had previously never changed their own insulin doses would do so if advice from the computer were available. The subjects cited avoidance of hypoglycaemia as their most important consideration, above the avoidance of long term complications. This perhaps explained their previous reluctance to experiment with insulin dose alterations whilst asymptomatic.

No subjects had any trouble understanding the user interface, many described it as "natural". The "Review" and "Notebook" facilities were greatly appreciated by all the subjects, although they agreed that the notebook alphabetical keyboard was cramped and it was difficult to enter any meaningful messages in the limited space of 24 characters.

From a practical viewpoint, the trial subjects considered POIRO to be a minimal intrusion on their normal lifestyle, although they did express some reservations over the size and weight of the EHT-10 prototype and would prefer a final model to be smaller. All subjects expressed confidence in the reliability of POIRO and said they would use such a device regularly in the future if it were available.

Trial Two

Trial 2 was carried out in May to July 1990. Again six patients were involved but in this case all patients had a two week run in period without advice followed by four weeks of advice and

then another two weeks with no advice. The same consultant physician was responsible for clinical support, a special diabetic liaison nurse recruited and educated the patients and the author provided the computers and the technical support. Several modifications were made to the program used in the first trial in order to improve the algorithms for insulin adjustment and to improve the reliability and security of data.

For trial one a fixed target fasting blood glucose of 5.5 mmol/l was set. It became apparent from analysis of results of trial one that setting a fixed target fasting blood glucose was too inflexible as inter patient variability in coefficient of variation meant that a "safe" target to avoid hypoglycaemia varied between patients. One subject who took part in trial one had a grade 1 overnight hypo, followed the next day by a grade 2 overnight hypo which caused her to withdraw from the study. The ultralente dose had been increased only once from the original value before the hypos. As no fasting blood glucose was entered on the day of the first hypo the algorithms had no reason to reduce the ultralente dose which remained the same. This then led to the grade 2 hypo. On further inspection, it became apparent that the fasting glucose had previously been high, which led the algorithms (quite correctly) to increase the ultralente dose; the fasting blood glucose was reduced to normal (5 mmol/l) very quickly by the increase. At the time of the first trial there were no rules included to reduce ultralente insulin in response to overnight hypoglycaemia or hypoglycaemia before breakfast, with no fasting blood glucose for confirmation. A rule to reduce ultralente by ten percent in case of any hypoglycaemia before breakfast was included after the first trial, along with more flexible methods for calculating target fasting blood glucose levels. The concept of a moving target fasting glucose was also invented for the second trial. The theory and implementation is described in previous sections of this chapter. It is a fruitful area for progress when more patient data is collected for analysis.

The notebook was also used far more in the second trial; when subjects entered hypos, unusually high or low blood glucose readings or insulin doses different to the advised dose, they were prompted to give an explanation for the events.

Results of the second trial were equally encouraging as those of the first trial, but for different reasons. Mean pre-prandial blood glucose levels were not reduced as efficiently but the rate of hypoglycaemia was reduced, both in terms of perceived hypos and blood glucose results below 3.5 mmol/l. The total number of reported hypoglycaemic episodes was surprisingly small which suggests that those patients who, nevertheless, recorded several low blood glucose values may not be aware of their own hypoglycaemia. This is a controversial issue amongst diabetologists and human synthetic insulin manufacturers and has been widely discussed elsewhere. So far there is little reliable evidence that human insulin reduces awareness of hypoglycaemia.

Higher variability of factors such as meal size and exercise level was also apparent in the second trial. One subject started her advice period by regularly recording a meal size of "Nothing" for breakfast. The subject explained that her normal routine prior to the trial was to inject her morning short acting insulin early and to eat much later (she entered a snack at this time). This misunderstanding of the system meant she was regularly advised to take no insulin and consequently exhibited much increased midday blood glucose results. She was advised to enter "Normal" at breakfast time if she was following her normal routine. She was also advised of the dangers of delaying food for more than half an hour after an injection. The same subject was also unlucky enough to sustain an insect bite which caused severe inflammation and consequently high blood glucose values. It is difficult to allow for ill health and stress in a trial of this kind where numbers are small, although these qualitative observations are important for future research work and serve as examples of the many problems which physicians encounter.

Other Significant Observations

Interesting observations were drawn from other users of the device who were not part of either of the clinical trials. The distribution of insulin was changed in some patients so that they had more insulin at lunch time. On questioning one patient it became clear that his main meal time was at midday not the evening meal as assumed by many physicians when initiating insulin

therapy. This example highlights the dangers of making too many assumptions concerning individuals in fitting them to the stereotypical patient.

Phase Plane Analysis and Possible Chaotic Behaviour.

In any feedback system, such as insulin/glucose dynamics, where the discrepancy between the desired glucose and observed value is used to adjust the strength of a negative feedback signal, i.e. insulin adjustment, the dynamics of the system are important. The approach to the end-point (in this case near-normoglycaemia) could be too slow or there could be regualr overcompensation, leading to oscillation or even unstable behaviour. One method of investigating this is to look at phase-plane behaviour (Rapaport 1977).

This project provided, for perhaps the first time, an opportunity to analyse diabetic outpatient data via the use of phase plane plots of insulin doses taken versus home monitored blood glucose. In an analysis screen implemented in the PMP program, the time series of insulin doses versus the following fasting blood glucose values were joined in chronological order by a dotted line if more than one day had elapsed between points or an unbroken line for time differences of one day. This pictorial analysis method gave an indication of possible optimisation to the optimum dose for normal events and a more mathematical analysis of the method should be developed. Due to the more variable nature of post-prandial blood glucose response to short acting insulin the method is probably more useful for the ultralente dose. An example plot is shown in fig 4.18, this shows the fasting glucose offset, or delta glucose, versus the previous dose of ultralente for the four weeks of dose adjustments made by POIRO for a single subject of the second clinical trial. The plot is typical of many subjects, it shows gradually increasing ultralente doses having little effect for some time until a large effect is present some four to five days after the initial increase. There follows an interesting spiral pattern which appears to have a focal point somewhere around the 50 unit mark.

This analysis thus raises important questions about both the dose adjustment strategy and the nature of the underlying physical characteristics of individual patients. The graphical

representation of the glucose response to insulin dose adjustments is a new method of education for patients and physicians. The method could successfully be applied in many other treatment adjustment fields and could, as stated earlier, provide evidence of whether individual patients have predictable variations and even predictable underlying diurnal variation, although the last of these claims is by far the most difficult to quantify and present separately from the background "noise" of physiological glucose dynamics.

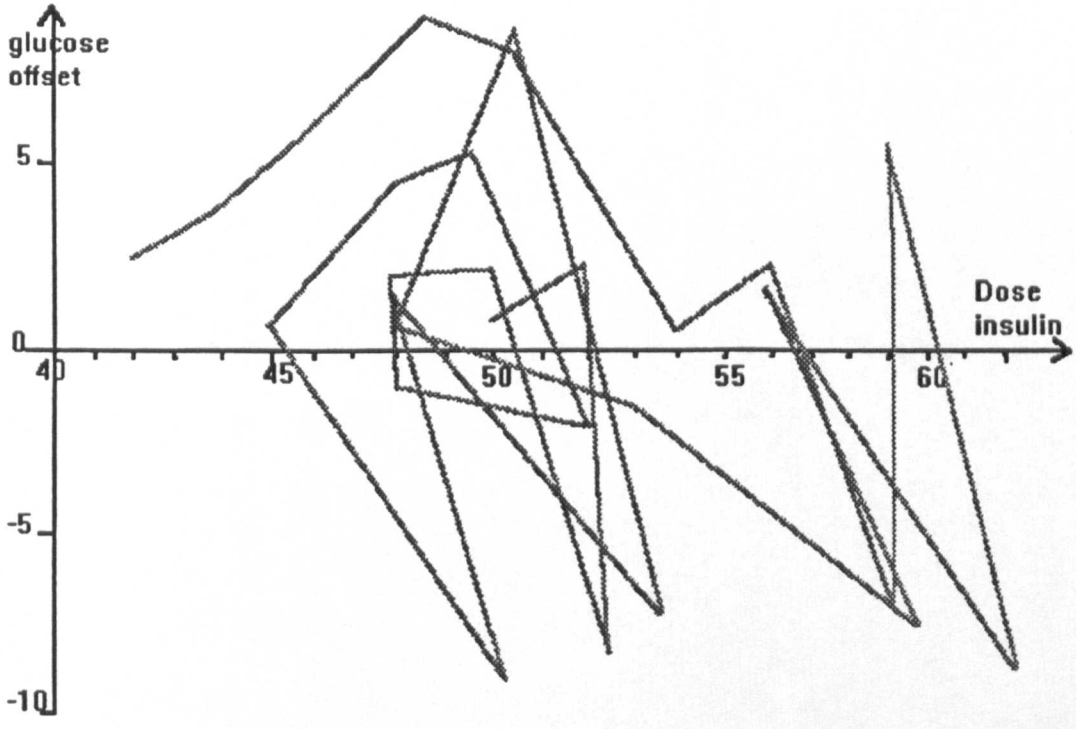

Fig 4.18 Phase plane plot of fasting glucose offset (measured value - target) versus the previous evening's long acting insulin dose for one subject during the second trial.

Phase plots of delta glucose versus the previous short acting insulin dose taken are far more variable and difficult to quantify due to changes in standard factors affecting the dose as well as the changes in the standard dose brought about by the algorithms. One method of analysis which has shown some pattern is to ignore supplementary insulin and to plot the standard dose versus the delta glucose. This shows that glucose levels vary differently for different patients (which is no surprise) and that the level at which an insulin dose change is effective is also a variable between patients. There may be a chaotic influence to the data, in which case there is no way of completely cutting down the variability. However, if this were the case, the assessment of when the glucose delta is outside the chaotic range which would provide optimum control is essential if insulin doses are to be altered at the right times. Thus, the limits to which blood glucose may be allowed to vary, which are used to set limits on the dose change curve should be set for individual patients and should depend on the chaotic attractor of the particular patient's previous blood glucose results.

Multivariate Analysis

Parameters for insulin supplements due to variations in meal size, expected exercise, current blood glucose and health are given approximate values based on available information and expert opinion (see table 4.10 above). It would be dangerous (as well as extremely difficult) for the hand held system to alter these parameters. The alteration of sensitivity parameters by the CAMIT system (Schrezenmeir et al 1985b - see chapter 3) resulted in problems of oscillatory behaviour of insulin doses and blood glucoses. The optimisation of these parameters is far better left to the physician management system when a sufficient amount of data has been gathered to carry out a statistically significant multivariate analysis.

Analysis of data from the first twelve patients has, however, been inconclusive. Coefficients of correlation between parameters have been high in occasional patients but no clear trends have appeared which would reliably point to automatic parameter optimisation of this kind.

SIMULATION.

The algorithms for adjusting glucose were evaluated by computer simulation. The basis of this simulation model of glucose metabolism was the minimal model of Bergman et al (1982) with modifications of Furler et al (1987). Further modifications were made to include injected insulin (Kobayashi et al 1983, Owens 1986) and ingestion of carbohydrate (Radziuk 1978,1985).

The basic code for the simulation of the metabolic pathway was produced using a metabolic simulation research tool - SCAMP (Sauro and Fell 1991). The compartmental approach converted into a suitable pathway type model for use in the SCAMP simulation tool. The code produced was used to repeat experiments from the Furler paper to validate the program and then the simulation code was integrated with the algorithms for adjustment. Modifications were made to allow repeated simulations of time periods in order to simulate an entire month of dose adjustments.

Other factors investigated included variability of meal times (using a Poisson distribution), relaxation of limits in dose adjustments and other factors which could not ethically be evaluated in the clinical setting.

Background

Simulation models of glucose metabolism fall under two broad headings: Comprehensive models and Simple models. Comprehensive models predict overall system behaviour under a variety of perturbations. The model is non linear and shows the crucial processes of glucose, insulin and glucagon dynamics and their interrelationships.

Simple models were pioneered by Bolie in 1961 (Berger and Rodbard 1989) but have not had a major impact due to their lack of sufficient detail. Further developments looked for models which could still be called simple but showed optimal complexity for modelling the system of

interrelationships. These so called minimal models are now widely used for non invasive evaluation of insulin sensitivity from IVGT tests.

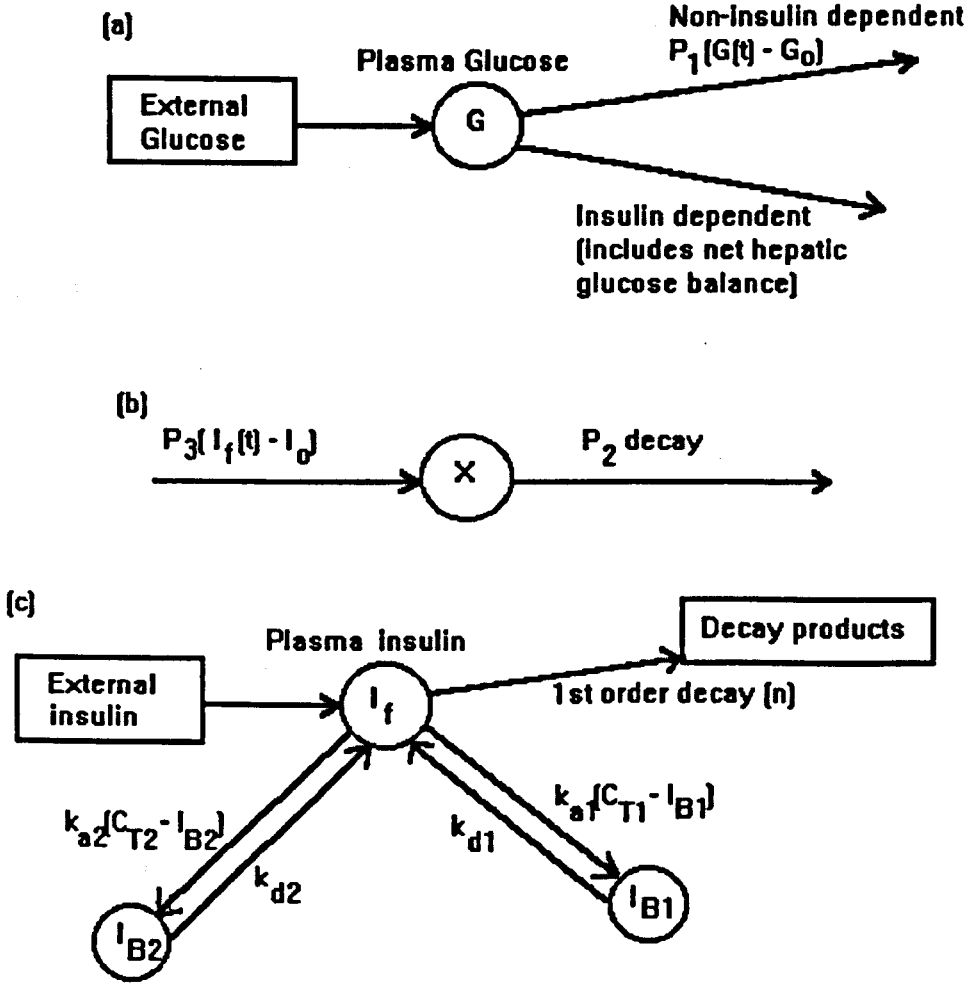

Fig 4.19 The simulation model (a) Glucose compartment, (b) Insulin-dependent rate constant X, (c) Plasma free insulin compartment, including a model of 2 types of anti-bodies. (see text).

Description of the Simulation Model

The simple model employed for these simulations consists of two compartments for plasma glucose and plasma free insulin (i.e. available insulin). The external source supplies glucose at a rate F_G which is divided by the glucose volume V_G. There are then two types of glucose disposal: non insulin dependent (taken up in red blood cells and the kidneys etc.) and insulin dependent (e.g. in muscles). This is described by an insulin dependent rate constant X. The available (or free) insulin I_F has one input F_1 and three disposal methods: decay, which is assumed to be of first order with parameter n and two reversible processes of binding to antibodies. Two types of antibody binding are modelled which were first proposed and validated by Berson and Yalow (1959). The set of differential equations derived from this model are (Furler et al 1985):

$$\frac{dG}{dt} = (P_1 - X[t])\,G(t) - P_1 G_0 + F_G/V_G \qquad \text{(E4.11)}$$

$$\frac{dX}{dt} = P_2 X[t] + P_3(I_F(t) - I_0) \qquad \text{(E4.12)}$$

$$\frac{dI_F}{dt} = F_1(t)/V_I - nI_F(t) - \frac{dI_{B1}}{dt} - \frac{dI_{B2}}{dt} \qquad \text{(E4.13)}$$

$$\frac{dI_{B1}}{dt} = k_{a1} I_F(C_{T1} - I_{B1}) - k_{d1} I_{B1} \qquad \text{(E4.14)}$$

$$\frac{dI_{B2}}{dt} = k_{a2} I_F(C_{T2} - I_{B2}) - k_{d2} I_{B2} \qquad \text{(E4.15)}$$

The parameters P_1 and P_2 are negative quantities. The model is constructed so that blood glucose tends to a reference value G_0 if the insulin level has its reference value I_0. The rate of change of the delayed insulin action term X tends to decrease as X increases and tends to increase as free insulin becomes elevated above its reference level I_0.

Parameter values for association and disassociation constants k_a and k_d, and total binding capacities C_T.were taken directly from Furler et al (1985). For a full description of the model refer to Furler et al (1985) and Bergman et al (1981).

This model of glucose metabolism was converted into metabolic pathways for use in the metabolic simulation tool SCAMP. The simulation model produced was validated against the published model's results using original parameter values. In order to utilise the model for testing the dose adjustment algorithms of POIRO several modifications had to made. First, the model included only constant infusions of both glucose and insulin, the equations subsequently employed for insulin absorption from sub-cutaneous injection and for glucose appearance after meal ingestion were incorporated in the SCAMP model using timed input equations.

The absorption of insulin was modelled using first order appearance and elimination rates in order to give an insulin concentration C at time t after a dose D, V_d is the apparent distribution volume of insulin (Kobayashi et al 1983).

$$C = \frac{K_a D}{V_d (K_a - K_e)} (e^{-(K_e t)} - e^{-(K_a t)}) \qquad \text{(E4.16)}$$

The parameters K_a and K_e in equation E4.16 were chosen for each type of insulin employed to fit with published results of insulin concentrations (Owens 1986). Only the two main types of insulin used in hand-held system trials were actually modelled (i.e. Actrapid and Ultratard). From actual data collected by the hand held device the distribution of meal times seemed to fit a Poisson distribution (fig 4.13 is again a typical example). Meals were, on the whole, quite regular, occasionally slightly early and occasionally late by up to two or three hours. The

distribution used for simulating day-to-day meal time variability exhibits this high probability within the first portion with a long tail after the normal meal time.

Simulation Results

With constant normal meal sizes, the dose adjustment algorithms quickly and smoothly reached optimum insulin doses and thus normoglycaemia. Variability of meal sizes produced a slightly longer time to settled doses; with large variability the doses did not settle down to a single dose but varied by differing amounts around a mean dose. Variability of meal times produced similar results, which implies that the system of allowing for meal time variability was satisfactory.

The results suggest that the algorithms lead to stable blood glucose values and do not intrinsically cause instability or oscillation. They are also stable with respect to quite high perturbations in meal timing and size.

Since the simulations were carried out, new data and models have become available. In particular, the model of Berger and Rodbard (1989) includes equations for insulin injections which take account of the amount of injected hormone in the calculation of the duration of action of the dose. This phenomenon is well known to exist and is included in Renner's basic rules of insulin therapy (ch. 3). However, the Berger and Rodbard model does not take account of insulin antibody binding as the effects are probably minimal with human insulins. Effects studied in the paper included a change of timing of the morning insulin dose and a change of insulin regimen. They concluded from these comparison studies that an optimal insulin regimen consisted of 3 short acting doses of insulin before breakfast, lunch and dinner with a dose of intermediate acting insulin before bed.

CONCLUSION

The hand-held system is a flexible and simple to operate unit which should provide optimum outpatient decision support for people with diabetes. The system has proved itself both in clinical trials and in simulation studies. Widespread clinical trials are essential to provide large amounts of data for the study of parameter setting by multivariate analysis. The limitations of the device with respect to general diabetes advice are not thought to be a significant problem. The more general advice expected by diabetics is best provided via a physician in a clinic consultation.

One of the major criticisms of all intelligent dose adjustment computers is that they rely on accuracy of blood glucose measurements entered by users. Studies by Mazze (1985, 1987) have shown the increase in reliability of patient reporting with the introduction of memory meters. It is of great importance that a blood glucose sensor which is quick and accurate should be incorporated in a future development of POIRO although there is little reason to disbelieve the blood glucose test results entered by any of the patients who have used this system. The problems of fabrication of insulin doses for psychological reasons is completely outside the scope of computer systems! Computers can help reasonably self-motivated individuals to achieve better glucose control in the easiest possible way with the minimum of intrusion on their normal lifestyles.

The use of a secure data storage medium, such as smart cards, is essential. If a modified form of POIRO is the answer, then the power ON/OFF switch should be modified so that the system is switched on by pressing it but can only switch itself off via the sleep facility of non-use for a specified time (say two minutes). This would ensure that data was backed up after every entry session and would save time at the next meal time.

The algorithms depend on intelligent parameter settings for their success. The parameters for calculation of the moving average fasting blood glucose targets may be calculated by analysis

of the probability distribution of previous values; the parameters for calculation of thresholds at which it is advisable to alter the insulin dose may be calculated using chaos analysis in the future and the parameters for calculation of supplementary parameters for multiplying doses for non standard factors may be done using multivariate statistical analysis. None of this analysis however is appropriate to be carried out within the POIRO system and the selection of parameters must be sanctioned by a competent, trained physician.

It is now a primary aim to provide decision support for physicians interested in the clinical care of diabetes who are not, nevertheless, diabetes specialists. The clinic-based POIRO managerial program has been successfully employed to set parameters by hand for some time and a logical progression of this is to develop a clinic based decision support system to help decide on these values.

The current managerial program has been modified to provide a subprogram of the new clinic-based system so that full compatibility of the systems is possible in principle. The new clinic-based decision support system is introduced in the next chapter.

CHAPTER 5 - THE PHYSICIAN-RELATED, CLINIC-BASED DECISION SUPPORT SYSTEM

INTRODUCTION

Between 1 and 2 % of the world's population has diabetes. With such a huge number of cases it often falls to relatively inexperienced physicians to decide what is the correct therapy for individual patients. Evidence shows (Gale 1990) that it is difficult for inexperienced physicians to decide which therapy to apply from diet therapy, oral hypoglycaemics or insulin. In developing countries, the problem is exacerbated by a relative or complete lack of facilities and medical personnel.

Although any decision support system would need to cover the whole gamut of diabetes therapy, from initial diagnosis through to complete insulin replacement therapy, the major decision support requirements of physicians fall in initialisation and adjustment of insulin replacement therapy.

Decision making is especially difficult when information provided by patients is incomplete, uncertain or missing. In especially difficult situations, hospitalisation of patients is the only option. However, by careful application of certain default rules of therapy, backed up by education and counselling by health care professionals, it should be possible to initiate and optimise therapy on an outpatient basis.

SYSTEM OVERVIEW

Decision making in diabetes management is provided by the PRESTO diabetes therapy decision support system. Physicians are prompted to enter information in as much detail as they desire; the system then makes suggestions about each section of the consultation as it progresses. At the end of the consultation, the system provides final suggestions for therapy adjustment. Help on how to use the system is available at all stages: the first stage of help describes how to enter

information, the second stage explains why the information is useful. The final therapy adjustments are justified by explanations built up during the consultation and a full audit trail of the consultation is provided on a summary card which may be printed automatically at the end of the consultation if required.

For insulin treated patients, an add-on module may be called (derived from the PMP ch. 4) which links with the POIRO patient-oriented decision support system described in chapter 4. This could, with further refinement, provide an integrated solution to diabetes therapy optimisation. Physicians will be able to set safe initial insulin doses, guided if necessary by PRESTO, which will be gradually optimised by POIRO between consultations. At the present time, this module is incomplete as it may only by used to initiate POIRO. Subsequent data retrieval and analysis still has to be done using the original stand-alone POIRO management program.

The POIRO system is an unusual and highly specialised device which has traditional algorithms at its core in order to exhibit "intelligent" behaviour, whereas the PRESTO system is built around much more traditional AI techniques but includes some novel features. It uses rules, facts and defaults for reasoning about knowledge. Semantic connectors and frames are extensively used in the design in order to simplify the rules and fuzzy variables are catered for in order to use more natural representation of knowledge.

The overall aim of the system is to provide decision support for inexperienced physicians who are faced with decisions about patients' diabetes therapy. As a side issue, the system also provides a data entry and data reduction facility: it provides an overview of each patient in simple terms and this could prove of value to other medical specialities, such as renal clinics, which are often required by diabetics.

The system provides a common structure to consultations so that no questions are forgotten or given less prominence unless physicians specifically leave out sections, which they are able to do if they so wish. However, the system is modular which allows the flexibility for each

section to be carried out individually in any order. The nature of questioning in medical consultations and the amount of time spent on each general area (weight, HBGM, complications etc.) has been studied (Taylor et al 1991) but no general principles have emerged about the relative importance of sections. Some general principles to guide the order of sections have been included but these may easily be changed by the physician.

A prototype system was developed very early on in the project and quickly made its way into the knowledge elicitation sessions. After completion of each consultation, the suggestions made by the system (if any) were shown to doctors who compared them to their own advice and made constructive criticisms.

Seminars were held regularly at which prototypes of the system were displayed to a group of physicians. Feedback was collected from physicians regarding the system's suitability of advice, the level of complexity and the improvements that could be made.

Selection of Development Platform

The PRESTO system's aims required a more wide ranging examination of development options. Both the selection of hardware and software was less restricted than the POIRO system. In the end, historical and practical considerations could not be ignored; however, the final selection would probably not have changed given different circumstances at the time.

The development of POIRO had been very confined to a small domain, whereas the PRESTO system had a much larger, and consequently less well-defined domain. This required a more flexible development environment that would permit incremental prototyping and a user interface that could be used by physicians.

The three possible platforms for software development in the desk-top computing field were identified as Sun Workstation running UNIX, IBM compatible PC under DOS, and Apple Macintosh. The important requirement of availability within the clinical setting restricted or eliminated the use of Sun and Macintosh systems and the PC option was therefore selected.

The eventual choice of hardware was an Elonex 386-based Lap-Top portable computer running under MS-DOS. The choice of software methodology lay between a development shell that had inference capabilities and a user interface building tool, or a low-level programming language. The domain knowledge acquired during the early stages of this section of the research pointed strongly towards a requirement for logical inference mechanisms with symbolic representation. A re-implementation, at this stage, of the inference capabilities of Prolog or more high level knowledge-base development methods was considered unwise as the system would probably be redeveloped at a later stage for wide-spread commercial development. For the development of a research prototype the platform selected was considered optimal.

There was also a tacit aim within the research to construct a decision support system for diabetes therapy with components which could, in theory, provide the foundation for a more generic application of decision support to other clinical domains. The main research issues to arise from this work include the representation of knowledge, the use of default reasoning and research into the problems of multiple decisions and their influence on each other. Reasoning by default and non-monotonic reasoning are relatively new ideas in AI which are addressed in the system in some sections; the use of these techniques could be more widespread, if necessary, in a production system.

KNOWLEDGE ELICITATION

Background knowledge

There exist many established medical outlines for physicians caring for diabetes (Hill 1987, Daly et al 1984, Olson 1981, Oakley et al 1978) and for insulin treatment of types I and II diabetes with the basal prandial regimen (Holman and Turner 1985, 1988). This makes the use of rule-based expert system technology particularly appropriate for decision support in the clinical setting.

Knowledge elicitation from the literature was mainly employed to identify the major functions for inclusion in a physician-oriented decision support system (Williams et al 1988). The eight functions which were identified are shown in an indented knowledge table (table 5.1).

Table 5.1 Diabetes therapy depends on:

- Patient history
- Current clinical status
- Current therapy
- Home glucose monitoring
- Clinic measurements
- Hypoglycaemia
- Diet
- Therapy administration

The adjustment of therapy depends first of all on what the current therapy is: whether it is diet alone, or one of the other therapeutic options. Table 5.2 lists the hierarchy of therapies, the major categories in the first column correspond to modules (or knowledge bases as they are termed) in the PRESTO system; the therapies are listed in order of increasing intensity. CSII (Pump) therapies are not listed as they are not appropriate to this decision support system and are still very uncommon.

Table 5.2 Therapy adjustment modules

- No current therapy (for newly diagnosed patients only)
- Diet therapy
- Tablets: divided into
  - Dexfenfluramide
  - Sulphonylurea
  - Biguanide
  - Sulphonylurea & Biguanide
- Tablets (usually sulphonylurea) & basal insulin
- Single insulin: divided into
  - Basal insulin only
  - Mixed insulin
- Multiple insulin: divided into
  - Short & intermediate acting (soluble isophane regimen)
  - Short & long acting (basal prandial regimen)

Adjustment of diabetes therapy seems to come down to a single basic equation (E5.1).

If control is inadequate then change therapy (E5.1)

This simplistic assessment does not show which factors are important; much more detail is, of course, required in order to assess such high level concepts as control. Table 5.3 shows the indented knowledge structure for level of control.

Not all the areas are required for every therapy type, therefore a further layer of influence is also shown; this shows that the therapy type precedes, and controls the decision to include any of the other information.

Table 5.3 Factors used to assess control.

Level of control depends on
- Hypoglycaemia
- Home glucose monitoring
- Clinic glucose measurements
- Biochemical analysis (e.g. Haemoglobin A1c)

Which of the above control factors to use depends on
- aim of therapy
- type of current therapy
- availability of the control factor

The type of therapy for newly presenting diabetics is decided at an initial consultation once diabetes has been diagnosed; the dependence of initial therapy on control factors is shown in table 5.4. Note that severely ill type I diabetics who present in ketosis or pre-ketotic state will almost certainly have been started on insulin replacement therapy immediately in hospital. Guide-lines for initialisation of insulin therapy for hospital in-patients are covered in Holman and Turner (1988) but are not included in PRESTO which concentrates solely on outpatient therapy initialisation and adjustment.

Table 5.4 Initial decision of therapy

Type of therapy depends on
- type of diabetes
- level of hyperglycaemia
- weight (or body mass index)

Type of diabetes depends on
- presence of ketones in blood or urine
- level of hyperglycaemia
- presence of islet cell antibodies

Opinions differ as to the most appropriate initial therapy for newly diagnosed, non-ketotic (type II) diabetics. The clinical management strategy used as a basis of the PRESTO decision support system is outlined in chapter 4, based on the guide-lines by Holman and Turner (1988). Therapy progresses in order of the list of possible therapies (table 5.2). Patients begin on no therapy and at the first stage are advised to alter their diet to one more suitable for their needs in relation to weight and glycaemic control (Lean and James 1986). If the fasting blood glucose is still high oral hypoglycaemic therapies are considered. The next step in overweight patients is usually metformin, followed by sulphonylurea or possibly both these agents together. After oral hypoglycaemic therapy has reached maximal levels and fasting blood glucose remains high, insulin may be applied either with a single daily dose of a long acting insulin or a single or twice daily dose of a mixed insulin. The most intensive therapy offered is multiple insulin injections; these consist of either short and intermediate acting insulin doses or long acting insulin with short acting insulin added to correspond with meals.

The choice of initial therapy in individual cases takes account of the fasting blood glucose, measured at the clinic, and the aim of therapy. The aim of therapy may be split into two categories: Exemplary control aims for fasting blood glucose levels and pre-prandial blood glucose levels within the normal range; i.e. 4-6 mmol/l. Less tight control aims to maintain the patient symptom free; this normally corresponds to a fasting blood glucose in the range 6-10 mmol/l. This choice depends very much on the context of the patient; such factors as age, coexistent morbidity and infirmity may be taken into consideration by the physician. PRESTO does not help with this decision as it was felt that many of the relevant factors would be impossible to quantify in any computerised system; it was also appreciated by physicians who did not wish to have decision support in this instance. In principle the decision could be aided but the extra complication and increased data entry required make it counter-productive.

By default, it is recommended that exemplary control is the aim for most diabetics whilst less tight control is appropriate for the elderly and those in dangerous employment where hypoglycaemia must be avoided at all costs (e.g. roofers).

Once active anti-diabetic therapy has commenced, the goal becomes the achievement of the designated aim of therapy. The adequacy of control is assessed from level of control and aim of therapy as shown in table 5.5.

Table 5.5 Adequacy of control
Adequacy of control depends on
aim of therapy
level of control

The enlargement of the vague statement on the right hand side of equation E5.1 to change the therapy is the main problem and forms the heart of this therapy adjustment decision support system.

SYSTEM DEVELOPMENT METHODS

A prototyping method of development was used. I attended and took notes at weekly diabetes clinics of three different types. One clinic was involved in a research study and followed mainly standard research protocols which give no room for flexibility within predefined "safe" limits of therapy (the UKPDS study). Therefore, all the information from these clinics was available in printed research protocols which indeed form an important part of the PRESTO system design process. The second clinic was carried out by the same clinicians but was not part of the research study. The third clinic was carried out by a different clinical department and was a standard NHS clinic.

There were several noticeable differences in policy and implementation between the three clinics. The major organisational difference was the timing of the clinic; the third clinic was carried out in the afternoon and was therefore unable to utilise a fasting blood glucose

measurement. The major policy difference between the two bodies of clinicians was the preferred choice of insulin regimen. The first body of clinicians were primarily using the basal prandial regimen whilst the soluble isophane regimen was used by the majority of patients who were seen by the other clinical department's clinicians. Many of the patients of this second clinical department also used premixed soluble isophane insulin. Home urine monitoring was not discouraged by this clinic, whereas patients seen by the first department's clinicians were recommended fasting blood glucose monitoring only, except for elderly stable patients. For several weeks, actual consultation sessions were monitored using a modified form of protocol analysis (chapter 2). With the cooperation of expert clinicians modes of operation were quickly established and elicitation of individual cases was carried out.

The amount of information which may be recorded in a diabetes clinic is enormous (Williams et al 1988). However, much of the information is not directly used for adjustment of therapy; for instance, the visual acuity. The knowledge content of data items may therefore be separated into items used for therapy adjustment decisions, items relevant to complications and items relevant for administration and research (such as family history, address and name of GP).

Regular clarification and further elicitation about points raised in the clinic was provided once again by the expert physician involved with the hand-held system. He acted as a knowledge tsar in choosing the level of information and type of representation to employ. A knowledge tsar is a heavily involved, committed expert who provides a final clarification in cases of disagreement among other experts, as suggested by others in the field of knowledge elicitation (Gammack and Anderson 1989, Davies and Hakiel 1988).

As well as specialist diabetologists, there are a myriad of supporting health-care professionals involved in diabetes care. Diabetes specialist nurses and dieticians provide probably the most important contributions to diabetes care after the specialist and GPs. Dieticians were interviewed (James, Eeley 1991) in order to establish guide-lines for dietary advice within the system. Consultations with dieticians at clinics also provided useful ideas for implementation

of the diet module. Diabetic liaison nurses were also consulted on a more casual basis in order to clarify points of relevance to therapy administration and patients' preferences.

The system specification has subsequently been divided into six operational knowledge bases contained in individual modules. The following sections contain the important principles for each of the modules for data entry and therapy adjustment decision support.

DIABETES THERAPY DATA ENTRY MODULES

Patient history module

This module has little relevance to therapy adjustment but has to be included for initial registration of patients and for subsequent identification and record keeping purposes. For adults, it will only be used in the initial consultation. For children, the height will need to be regularly updated. In the future, such information could be retrieved directly from a computerised patient record, which may be either card-based or sent by patients' GPs over networks.

The general information entered is name, hospital number, gender, address and occupation. Then more specific information about the mode of presentation of diabetes is entered. The information should only need to be entered for new patients; it may then be archived for retrieval at subsequent clinic visits. The only items of relevance to therapy are the type of diabetes and the patient's height.

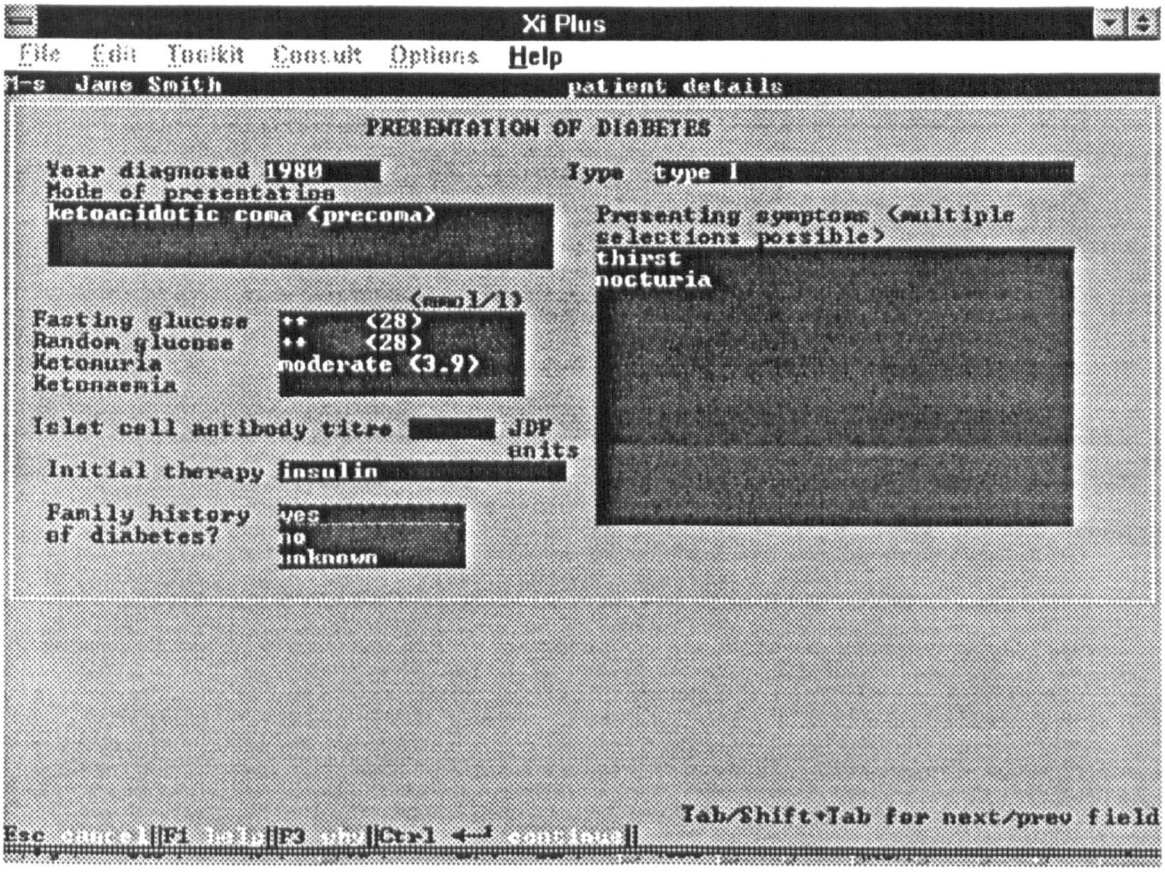

Fig 5.1 Initial data entry information displayed on the summary screen. This is normally entered once only.

If type of diabetes is not explicitly entered, it is inferred from information about presenting ketones, islet cell antibody titre or hyperglycaemia. At present, this inference is only carried out if the type of diabetes is declared to be unknown; there is no check within the knowledge base for inconsistencies. It should be emphasised that the PRESTO system does not carry out diagnosis but is concerned solely with the management of diabetes. Height should be stable in adults and is therefore entered only once at the patient history stage. For younger people height may be entered under the next module "current clinical status".

Current Clinical Status Module

This module covers high level details of the patient's current clinical status. It should be the first module to be executed in follow-up consultations. The most important piece of data entered at this time is weight which, like height, may be entered in metric or imperial units. The most common symptoms of hyperglycaemia are listed and may be selected if they are present. If symptoms are present, therapy is inadequate and the rules within individual knowledge bases ensure that advice is given to increase therapy.

An assessment of obesity is required in order to determine a preferred diet. The weight and height of patients may be used to calculate various measures of obesity, such as the ratio of weight to ideal body weight (Metropolitan life tables), or the body mass index (BMI). The latter of these is the current preferred assessment of obesity as it is independent of gender. BMI is used to categorise obesity level (table 5.6) by the World Health Organisation (W.H.O.). The equations for calculation of ideal body weight (IBW) are given in equations E5.2 and E5.3. The formula for calculating the BMI (or Quetelet's index as it is also known) is given in equation E5.4. For the BMI weight is given in kg and height in metres; for the IBW, weight is given in kilograms and height is in centimetres. The BMI has the advantage of being gender independent, although in the past more attention has been paid to the ideal body weight.

$$IBW = -0.98 \times Height + 0.0049 \times Height^2 + 89 \quad \text{(Male)} \qquad \text{(E5.2)}$$

$$= -0.79 \times Height + 0.0044 \times Height^2 + 68 \quad \text{(Female)} \qquad \text{(E5.3)}$$

$$BMI = Weight / Height^2 \qquad \text{(E5.4)}$$

Table 5.6 W.H.O. Categorisation of obesity from BMI

BMI	Obesity assessment
< 20	Underweight
20 - 25	Normal weight
25 - 30	Overweight
30 - 40	Obese
> 40	Morbid obese

Research has shown (Turner et al 1982) that the degree of obesity is a crucial factor in determining insulin requirements of diabetics treated with insulin, be they type I or type II. The insulin requirement may be calculated for a standard (72 kg male) patient then multiplied by a simple factor which has been given the name "F value". The F value equations are given for males and females in equations E5.5 and E5.6

$$F = \text{Weight}/(14.3 \times \text{Height}) - \text{Height} \quad \text{(Male)} \qquad \text{(E5.5)}$$

$$F = \text{Weight}/(13.2 \times \text{Height}) - \text{Height} \quad \text{(Female)} \qquad \text{(E5.6)}$$

The six most commonly found complications of diabetes: vascular, retinopathy, autonomic neuropathy, peripheral neuropathy, nephropathy and feet problems are then covered in overview. The presence of retinopathy is a factor in therapy adjustment as it has been shown that retinopathy progresses more quickly if diabetic control is tightened quickly; other complications have no direct relevance to therapy adjustment.

Social history of smoking and drinking is important and is asked early in the consultation. Smoking does not have a direct affect on the choice of anti-diabetic therapy, but should be discouraged as people with diabetes are more at risk than people without diabetes from the common conditions influenced by smoking such as cardiovascular disease. Alcohol potentiates certain sulphonylurea drugs and, if taken to excess, may contraindicate metformin. In addition, the blood glucose is affected by the carbohydrate content of alcohol and its effects may disguise hypoglycaemia. It is common for hypoglycaemia to follow some hours after excessive alcohol. Advice should be to avoid alcohol if possible, but if not, then take it in moderation. Practical advice to a heavy weekend drinker may be to reduce insulin doses to compensate for the effects of alcohol, the amount of adjustment will have to be found by trial and error by the patient.

Finally in this module, the aim of therapy is entered. The default aim is exemplary control, but the aim may be changed at any time during the consultation or in subsequent consultations, in order to check the effect of aim on therapy adjustment.

Current Therapy Module

The current therapy options are listed as the first column in table 5.2; once a selection has been made, the second level is assessed by inference from entry of actual insulin formulations or hypoglycaemic tablets used.

For instance, if a patient 's therapy is entered as "multiple insulin", the types of insulin taken are then entered as "Insulatard" and "Actrapid". The inference is then made that the patient's insulin regimen is the short and intermediate regimen (or soluble isophane as it is commonly referred). There is a known problem with this inference in that if no insulin types are entered the system stops.

For insulin therapy, the current doses taken by the patient need to be entered for each type. For tablet therapies it is only necessary to ask whether the dose is maximal or sub-maximal; this should be based on the maximal *tolerated* dose, absolute limits of each tablet type should be recorded for use if the physician wishes to check the maximum dose of any individual tablet.

Diet Module

This module covers general dietary advice, as well as specific advice relevant to the type of diabetes. Two levels of assessment of diet are possible: detailed and overview. A detailed assessment involves questions about the type of foods eaten at each meal throughout the day, followed by suggestions on how to modify the diet. The overview assessment option permits information to be entered in a much higher level form. The distribution and size of meals through the day are the important criteria. The size of meals may be in portion sizes or in grams of carbohydrate if the patient has been formally assessed by a dietician and is following a calorie controlled diet.

The module records weight trend and patient assessment of adequacy of diet. These figures are used in the decision about whether to begin active therapy for diet treated individuals or to refer to a professional dietician.

An option is available for a computerised diet prescription; this is based on the algorithms of Lean et al. (1986) and comprises an assessment of the daily energy requirements or basal metabolic rate (BMR). BMR is related to a patient's ideal body weight (Metropolitan Life Insurance) as calculated in the current clinical status module. A correction for activity is used to calculate individual energy requirements. Once energy requirements are known, proportions of complex carbohydrate, fats and protein are calculated in the ratio 50:35:15 of energy requirements. This is a decrease in the proportion of carbohydrate suggested by Lean but is a more realistic target for most diabetics (Eeley 1991) who have to omit any simple carbohydrates such as sugars from their diet. Actual grams of each component are calculated by division by the energy content of one gram of each of the components. The equations for calculation of calorie requirement may be found in the paper by Lean et al. (1986).

The use of basal metabolic rate (BMR) for calculation of dietary energy requirements has been criticised as excessive (Daly et al. 1985). This has led to the proposal of the sedentary daily expenditure (SDE) as a base for estimation of energy requirements (Webb and Sangal 1991). The SDE method remains to be thoroughly clinically assessed but appears to produce more accurate predictions when fat free mass is known. However, the estimation still fares well even with an estimation of fat mass made using an equation similar to that for BMI but with a smaller exponent than 2 for the power of height. The equations for SDE are given (E5.7 and E5.8) and may be substituted for the BMR calculations in the estimation of dietary requirements to improve the estimate if it is so desired.

$$SDE = 28 \times Weight - 31 \times (Weight/Height^{1.6}) + 939 \qquad \text{(men)} \qquad \text{(E5.7)}$$

$$SDE = 21 \times Weight - 27 \times (Weight/Height^{1.8}) + 1053 \qquad \text{(women)} \qquad \text{(E5.8)}$$

The physician may select from three aims of diet: weight gaining, weight maintaining or weight reducing. It is recommended (Lean) that a maximum of 500 kCals may be deducted or added to the basic energy requirements calculated in order to provide steady weight loss or gain of approximately 2 kg per month.

Finally, a reminder that these nomograms provide merely an assessment of the total dietary needs of an individual. Professional, detailed dietary analysis by a trained dietician is desirable on a regular basis.

Home Glucose Monitoring Module

This module may be subdivided into urine glucose monitoring and blood glucose monitoring. The method of home blood glucose monitoring assessment is selected from a list which includes visually read strips, reflectance meter and Exactech meter. If doubt is later inferred about the accuracy of HBGM then PRESTO suggests a more accurate measurement technique if possible, or to corroborate the home glucose tests with clinic tests and long term assessments such as the HbA1c.

Different methods for physician data entry are essential. Physicians do not show much enthusiasm for transcribing an entire log book to the computer. Even numerical assessments of the mean and standard deviation are not intuitively appealing to many doctors. A more common method of expressing an overview of log book readings is by a range, defined to contain the majority of readings, or else an overview of pre-prandial blood glucose levels in symbolic linguistic terms.

Assessment of regularity and adequacy of HBGM is related to entry of the mean number of days per month on which measurements are recorded and the mean number of readings per day. It is recommended that patients on full insulin therapy should monitor four days each month, and take four blood glucose readings in each of those days. Other, less intensively treated patients are adequately monitored by one fasting blood glucose test per month once relative

stability is achieved. It is stressed that illness perturbs the blood glucose in all diabetics and more frequent (ideally daily) monitoring should be carried out during any intercurrent illness.

Home blood glucose monitoring values may be presented at the clinic in one of three ways: A log book of values, word of mouth or memory meter/computerised log book.

Computerised log books or memory meters should have the capability of displaying at least some indication of overall control. Either a mean pre-prandial value over the previous month, or seven values for example (Glucometer M), or a simple graph of mean daily glucose and/or mean glucose levels for each time of day (as done by the hand-held system described in ch 4). Ideally, physicians should also have a personal computer with facilities for communication with all the HBGM devices now on the market in order to transfer the data for interpretation by various statistical and graphical methods.

Problems arise with interpretation of patients conventional paper log books. There may be a lot of data or just a few scattered points. In essence, what is required of the physician is an assessment of the level of blood glucose before each main meal and before bed.

The expression of pre-prandial blood glucose values in linguistic (or fuzzy) terms allows physicians to give an overview which does not rely on actual numbers. The range of possible terms is low, normal, high and very high. Guide-lines are given in the help section but it should be easy for physicians to decide into which category the test results should fall by intuition.

For more numerically inclined physicians, HBGM values may be entered as mean and standard deviations, range values, or entire sets of readings. However, the computer merely converts these numbers into the same fuzzy terms. However, actual levels of blood glucose are used for precise calculation of therapy adjustment.

Clinic Measurements Module

This module prompts for observations and tests carried out in the clinic and laboratory results. Blood glucose and urinalysis measurements should be routinely carried out in the clinic. Clinics are best held in the morning so that patients can come fasting. The glucose at other times of day (e.g. after meals) is highly variable. The random glucose, as it is called is better than no indication at all in type II diabetes but is not accurate enough for adjustment of therapy in type I diabetes. The clinic fasting glucose may be used alone to alter therapy for type II diabetics. Its use for type I diabetes is merely as a confirmation of the HBGM results reported by patients. It is recommended that all patients have regular checks for progression of diabetic complications: In particular an annual review should be carried out at which the items in table 5.7 should be examined.

Table 5.7 Annual review - items to be examined

Blood pressure
Visual acuity
Fundoscopy
Foot examination
Cholesterol and triglycerides

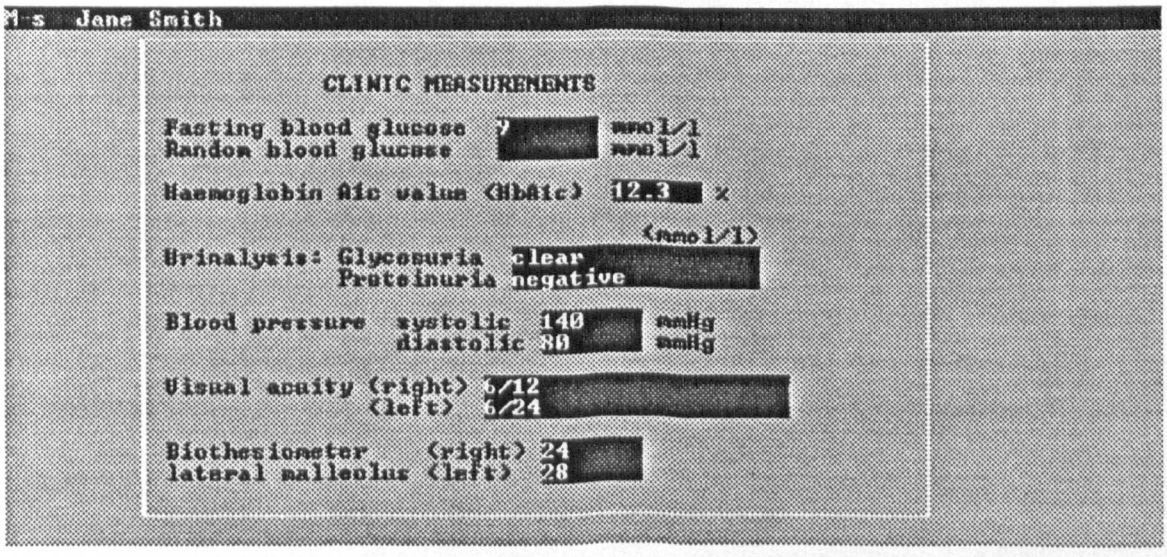

Fig 5.2 Clinic screen, showing biochemistry and examination data entry form.

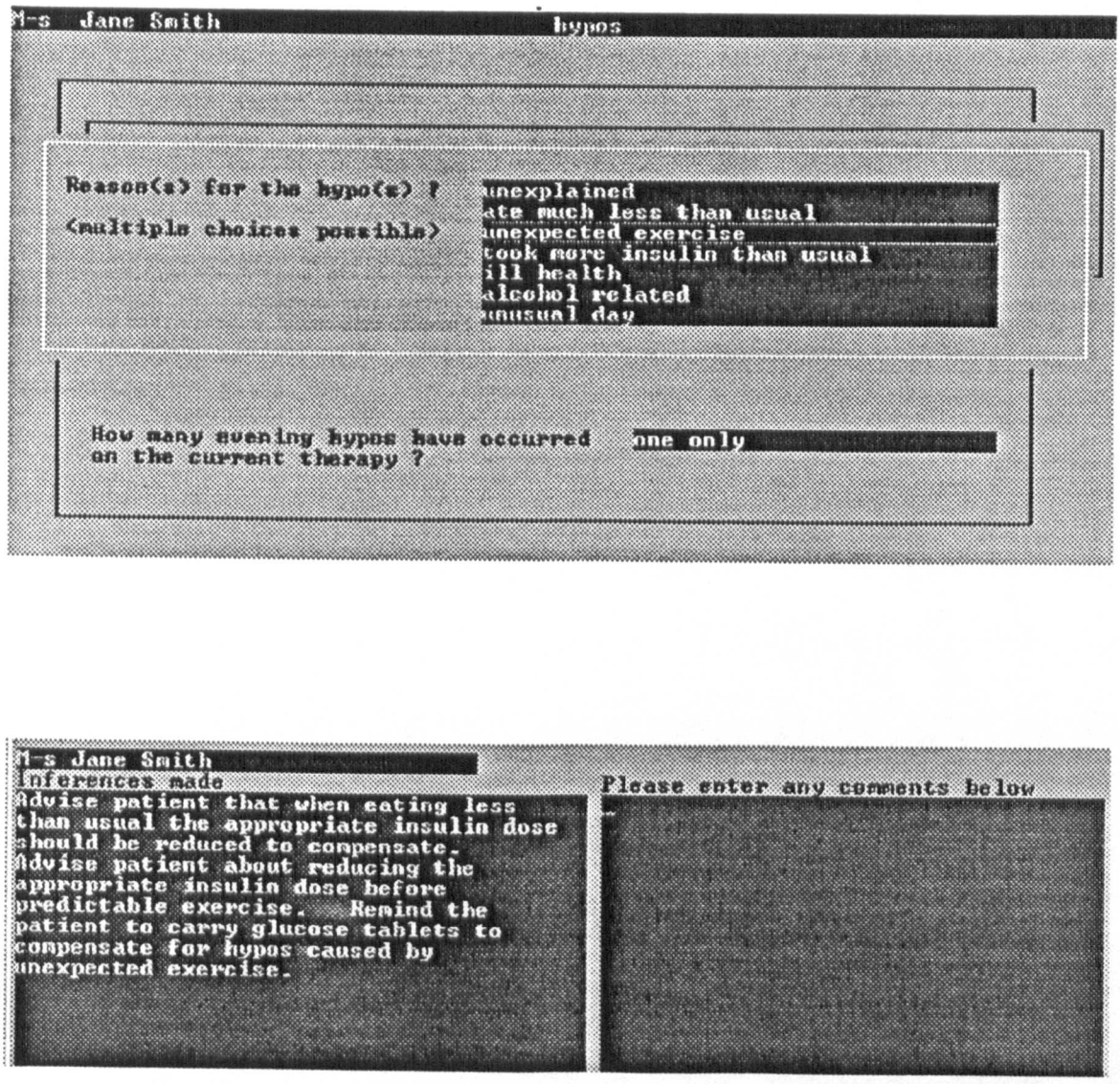

Fig 5.3 Hypoglycaemia module screens. Dat entry screen (top) and advice offered (bottom).

If examination of any of the data entered so far is suggestive of complications such as renal dysfunction or hepatic problems then the decision support system notifies the physician. Further test results which may be entered for assessment of complications include those in table 5.8

Table 5.8 Biochemical analysis

Plasma Creatinine	
Creatinine clearance	(24 hour)
Protein clearance	(24 hour)
Potassium	
Sodium	
Uric Acid	

It is not within the current scope of the system to advise therapy for any of the complications presented but the system informs the physician when the level of any test is abnormal and an appropriate course of action. An example of how the above data may be used is the use of plasma creatinine to estimate renal function and the onset of nephrotic syndrome. Once plasma creatinine becomes abnormally high (above 150 mg/dl), the inverse of the plasma creatinine plotted against time should show a linear relationship. By use of a few timed creatinine results it should be possible to estimate when a renal physician should become involved and to estimate the time before active therapy should be considered (Matthews, personal communication).

Hypoglycaemia Module

The presence of hypoglycaemia (hypos) tends to overshadow other factors in therapy adjustment decisions as the avoidance of hypos tends to be uppermost in most patients' minds. In order to properly adjust therapy, physicians first need to ascertain whether the hypo could have been prevented by dietary adjustment or insulin reduction. The timing of hypos in relation to meals and insulin doses is used to decide which insulin dose to alter or how to adjust the diet to avoid further hypoglycaemia. In cases where there is an explanation for a hypo, for example

if they are exercise-related, suggestions for avoidance of hypos are given, for example to reduce a short acting insulin dose prior to exercise.

Therapy Administration Module

This module is mainly concerned with insulin administration but also questions timing of tablets for tablet therapies. Short half-life, second generation sulphonylureas may cause hypoglycaemia in the morning; the tablet may then be moved to lunch time. The time of taking tablets is questioned and may be used in the therapy adjustment module later to propose a change to avoid further hypoglycaemia or low pre-prandial blood glucose results.

Various problems may be presented by patients concerned with insulin administration by injections. Areas covered by this module include problems at injection sites, mixing of injections and timing of injections. There are four recognised problems which may occur at injection sites: lipoatrophy - the wasting away of flesh around sites, lipohypertrophy - lumpy deposits of fat, insulin allergy - a red, itchy rash near injection sites and abscesses caused by non-sterile needles.

PRESTO identifies the problems and gives advice for alleviation of them. The treatment suggested for the first two problems is usually rotation of injections sites. Allergies may require a change of therapy to insulin of a different species if they persist. Abscesses may require surgical removal and treatment. PRESTO will suggest alternative therapies within the therapy adjustment modules if necessary.

Timing of insulin delivery with meals has been extensively investigated (Kraegen et al 1981, Schrezenmeir et al 1985b). The optimal time of insulin delivery is regarded as 30 minutes before meals and this is the advice suggested by PRESTO. Periods longer than 30 minutes have been tried by other researchers but pre-prandial hypoglycaemia has been produced.

DIABETES THERAPY ADJUSTMENT MODULES

This section is subdivided into individual therapy-related modules which are called into operation depending on the entry of current therapy.

"No Current Therapy" Module

The selection of initial therapy is made along guide-lines set out by Holman and Turner (1988). It is recommended that a period of at least three months intensive diet therapy should be tried in all non-ketotic patients before any active therapy is initiated (UKPDS protocol). The selection of subsequent therapy is made on the basis of the aim of therapy and the actual blood glucose level either monitored at home or at the clinic is used as the basis for this decision.

Diet Therapy Adjustment Module

The term "diet therapy" is employed to describe the treatment of type II diabetes when the glucose level is high in conjunction with obesity and no other therapeutic agents are required to bring the blood glucose back to normal levels. As outlined above, however, diet is an essential aspect of all diabetes therapy. The aim of diet therapy is to educate patients to eat a more appropriate diet, as outlined above and ultimately to lose weight. Realistic target weights need to be set which patients have a reasonable chance of achieving. As a rough guide a weight loss of 2 kg is approximately equivalent to a 1 mM decrease in fasting blood glucose.

If the diet is not working, or the blood glucose remains persistently high, the module decides the next therapeutic option: tablets or insulin. The basis for this choice rests, once again, in the aim of therapy and level of glucose. Other factors such as alcohol intake, presence of certain complications etc. also play a part. In particular, Metformin must not be prescribed when there is evidence of hepatic or renal failure due to the increased risks of lactic acidosis.

Drugs which are said to have a weight reducing effect, such as dexfenfluramine hydrochloride, are sometimes prescribed for overweight type two diabetics but their use is controversial and should preferably be avoided (BNF March 1992, p160). Such drugs are therefore not currently included in the diet therapy module.

Oral Hypoglycaemic Therapies Module

The choice of initial oral hypoglycaemic therapies is limited to two major options: sulphonylurea or biguanide (Metformin). All currently available sulphonylurea drugs have been included as options within the system.

The rules for adjustment of oral therapies should be based solely on fasting glucose measurements taken before breakfast: these measurements are unaffected by meal times and provide an accurate indication of the level of glycaemic control. The major rule in this case is " If the fasting glucose is above the target range then advise an increase in therapy".

In conjunction with this, there are rules for switching to insulin therapy if the maximum oral therapy is ineffective (see above for definition of maximal therapy): "If the fasting glucose is above the target range and oral therapy is maximal then advise switch to insulin therapy".

The rules for increasing oral therapies depend on the aim of therapy: If the aim is exemplary control then oral therapies will be applied only if there is a realistic chance of the glucose falling to near normal levels of around 6 mmol/l, otherwise insulin is advised to be initiated immediately. In some elderly patients who have no complications, less tight control may be acceptable and oral therapies may be continued while they have no diabetic symptoms.

There exists a grey area between starting oral therapy with a certain dose and stopping oral therapy to start insulin therapy once maximal therapy is ineffective. There is no simple relationship between the amount of tablets and their effect. Rules of thumb for incrementing tablets were thus elicited and are employed for individual tablet types. Problems of different

tablet sizes have to be taken into consideration, especially with the more potent sulphonylurea tablets such as Glibenclamide. An example strategy for Metformin is given in table 5.9. Tablet sizes of Metformin are 500 and 850 mg. The smaller (500 mg) tablets are often used as a "start up" dose by non-experts but are not advised by experts. The British National Formulary (BNF 1992) contains advised protocols for drug therapy which may be added to the system for any new oral hypoglycaemic drug as it appears.

Table 5.9 Strategy for incrementing Metformin.

Initial dose	850 mg	
If FBG still high	1700 mg	
and then	2550 mg	(Maximum dose)

When the decision is made to stop sulphonylurea tablets and start insulin therapy, an adjustment of the fasting blood glucose (FBG) has to be made to allow for the effect of maximal sulphonylurea (equation E5.9 a and b).

$$FBG = 4.5134 \times 10^{(FBG \times 0.0426)} \quad (FBG <= 16mM) \quad (E5.9(a))$$

$$FBG = 20 \quad (FBG > 16mM) \quad (E5.9(b))$$

Decisions also have to be made whether to stop the sulphonylurea or suggest that it be continued in addition to a basal insulin supplement. Once again, the decision is based on the fasting glucose level.

Insulin Replacement Therapy Modules

As already stated, the area in most need of decision support is insulin therapy adjustment. This falls into two levels of adjustment: Choice of regimen, adjustment and optimisation of the chosen regimen. The former decisions are general to all therapy adjustment modules whereas the adjustment and optimisation of an insulin replacement therapy regimen is specific to the current therapy regimen.

Elicitation of the general principle of insulin adjustment had already been carried out in the design of the patient-oriented system. The rules used for that system were suitably altered to suit the outpatient clinic basal prandial module. The main difference was the higher level of dose changes suggested. Whereas in the day to day changes made by the patient-oriented system the maximum permitted increase in dose was 5% the minimum sensible dose change in the clinic system was 10% with a maximum change of 40% except in exceptional circumstances (Matthews 1991, personal communication).

KNOWLEDGE REPRESENTATION

Representation of time

The knowledge representation structures are related primarily to times of day. These are split into 8 parts: 3 meal times and between meal periods (table 5.10).

Table 5.10 Meal times and periods between meals

breakfast	-	the first meal of the day.
morning	-	the time between breakfast and
midday meal	-	variously called lunch, dinner etc. by patients
afternoon	-	the time from midday meal to
evening meal	-	variously called dinner, supper etc.
evening	-	the time period until
bed	-	this is the time when most patients take a snack and maybe long acting insulin
overnight	-	the time between bed and breakfast.

Temporal relationships are defined in order to link these time points; e.g. successor of breakfast is midday meal. Other information is related to these times as follows: Insulin doses are related to meals by, for example, dose of short acting before *Meal* (e.g. breakfast). Snacks between meals are represented as: Snack in *morning*, hypos are related to their time of occurrence by relationships such as: Hypo in *afternoon* includes *occasional* (number), *grade 1* (severity), *exercise-related* (cause).

The connecting words (connectors) "*before*", "*in*", "*of*" and "*includes*" are used to build up structures which may be used in generalised rules using variable time periods and meals.

Representation of Insulin Characteristics

As many of the thirty or so insulin formulations share similar characteristics of duration of action, use and nature, the rules may be generalised to some extent and a hierarchical frame structure is employed for the representation of therapeutic agents. The oral agents are also represented in this way. An example for the short acting insulin Actrapid™ is shown in table 5.11

Table 5.11 Characteristics of a type of insulin (Actrapid™)

Actrapid is a short acting insulin
species of Actrapid is human
onset of Actrapid = 30 (minutes)
duration of Actrapid = 360 (minutes)
manufacturer of Actrapid is Novo

Additional information may then relate to this knowledge structure. For instance insulin levels may become very high on some pork-based insulin formulations due to the presence of antibodies, antibodies are not likely to affect synthetic human insulin levels, so it may be advisable to change to a human insulin. In another case, patients who are prescribed human insulin may experience undetected hypoglycaemia, they could be changed to pork-based insulin again.

The manufacturer is included for cases where a second insulin formulation is required, for instance the addition of short acting insulin to a long acting insulin. It may be more appropriate to prescribe insulins from the same manufacturer and species to avoid problems of supply or allergies etc.

SYSTEM IMPLEMENTATION

The system is implemented as a series of modules. In an initial screen, the entry of the patient's name and hospital (or some other) identification number begins a search for any previous history. If previous history exists, it is retrieved and displayed in a condensed format for the physician. This format is an attempt to carry out a concise clinical summary, inferred from the previous history items. An example summary of a fictitious patient is shown in fig 5.4.

If no previous patient history exists, the system loads the module that elicits patient history, which then asks for details of the patient's background and in particular asks about the presentation of diabetes. The other areas within the system may then be entered in an order selected by the physician, but guided by the decision support system. A default order is recommended as: (1) current clinical status, (2) current anti-diabetic therapy, (3) HBGM, (4) clinic test results, (5) hypoglycaemia, (6) diet and (7) therapy administration.

Once all relevant information has been entered, the system automatically executes the appropriate set of rules for the current therapy type and advises the physician of its suggestions. The physician may then type in free text comments. A printer may then be used to print out a summary of the consultation, this lists all the important data entered along with the computer's suggestions and the doctor's comments.

If required, the physician may request therapy suggestions at any point once the current therapy has been entered into the system by the selection of "advise therapy suggestions" from the main menu. The physician may also return to any of the sections and change any of the information already entered. The system may then advise different suggestions depending on what information was changed. For example the addition of extra blood glucose test results may fundamentally change the suggestions.

The Development Shell - Xi+

The structured representation system and symbolic reasoning employed within this design fits very well with the knowledge based system building shell Xi+™. In the Xi+ expert system shell, rules which may be used in forward chaining are called demons; in order to differentiate between demons and rules the key word "If" is replaced by the word "When" in demons. Demons are not used in backward chaining but it is possible to use rules in both forward and backward chaining although this may prove complicated and it is clearer if rules and demons are kept separate. Therefore, the normal "If" type rules are used solely for backward chaining.

This separation into "rules" and "demons" is useful for extracting procedural knowledge about which modules to carry out in a certain order from the more declarative knowledge used to represent knowledge about diabetes and its treatment within the individual knowledge base modules.

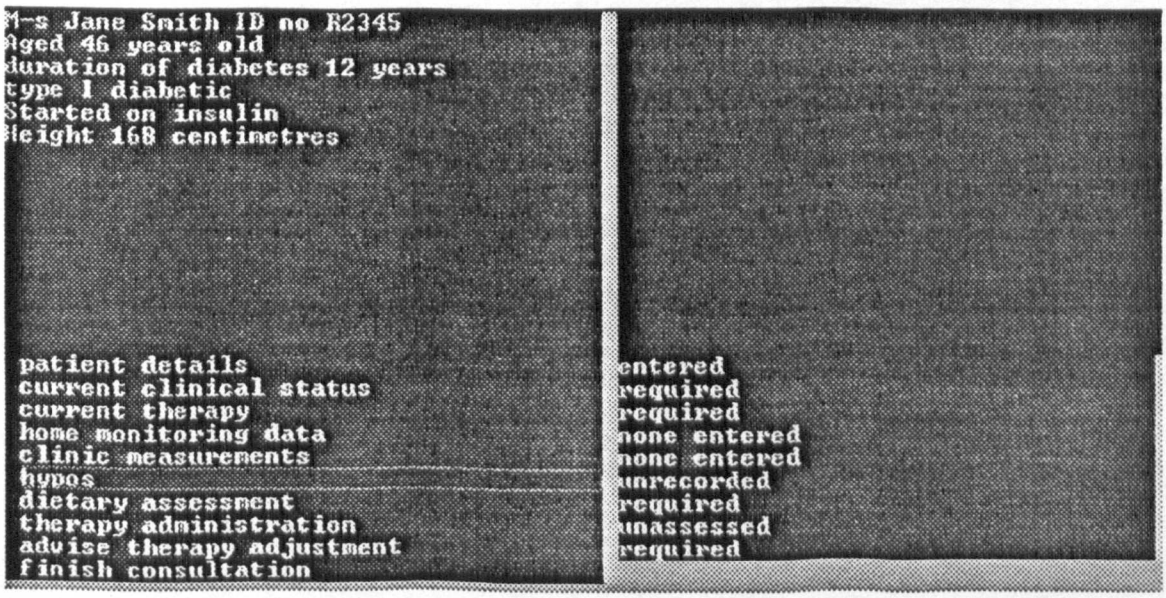

Fig 5.4 Patient history summary (top left) and main menu of options(bottom left) and their status (bottom right), at the start of a consultation.

Functionality of the System

A main "driver" knowledge base suggests the above options to physicians in the specified order although the information may be entered in different orders for different patients. One observation from the clinical setting is the seemingly unstandardised and unstructured nature of questioning by many physicians. However, the physicians' methods showed that they were moving between the above well defined sections in a logical order for particular consultations. An area of interest may be how to model the direction of the consultation in different circumstances and the benefits or drawbacks of a more structured, predefined route through the data entry procedures.

Once sufficient information has been gathered, the controlling knowledge base calls a therapy regimen knowledge base. This then assesses all the available information, specific to the current therapy, to produce therapy decisions. In most cases a single recommendation strategy is suggested, although occasionally alternatives are given for the physician to make the final decision.

Using Default Insulin Requirements

Insulin requirements undoubtedly vary with many different factors. The most important known factors are given in table 5.12.

Table 5.12 Insulin requirements

Insulin requirements depend on:
- remaining beta cell function (endogenous insulin secretion)
- degree of obesity
- duration of diabetes
- diet and exercise profile

As the production of insulin is equimolar with the production of C-peptide (chapter one), and C-peptide is fairly stable, it is possible to estimate surviving beta cell capacity by an assay of C-peptide. For people with very little endogenous insulin secretion, i.e. those with type I, insulin-

dependent diabetes, the insulin requirements may be estimated, without any blood glucose values, by use of the F-value (E5.5 and E5.6) and the experimental and empirical observation that a male of average height and weight requires 36 units of exogenous basal insulin (see Holman and Turner 1988). Equations E5.10 and E5.11 give values for basal and pre-prandial insulin needs in terms of the F-value parameter.

Research on normal and diabetic subjects, (Holman and Turner 1988) has shown that, in normal circumstances, slightly more insulin is required at meal times (54% of total insulin need) than is required to meet the basal needs (equation E5.11). In practice, experts often aim to balance the amounts of long and short acting insulin.

$$\text{Basal insulin need} = 36 \times F \qquad \text{(E5.10)}$$

$$\text{Pre-prandial insulin need} = 54/46 \times \text{Basal insulin need} \qquad \text{(E5.11)}$$

For type II diabetes, once insulin therapy becomes necessary, the fasting blood glucose (FBG), combined with the F value (F), indicates the basal insulin need (equation E5.12). In most cases, once the basal dose exceeds "16 x F" units insulin production is so low that extra insulin is needed to cover meals. There is no simple ratio to predict meal time insulin requirements; the need for pre-prandial insulin increases as the beta cell function decreases and basal need increases towards the expected maximum. The initial pre-prandial insulin need is calculated from the basal insulin dose by equation E5.13.

$$\text{Basal insulin need (B)} = (3.22 \times FBG - 0.07 \times FBG^2 - 11.11) \times F \qquad \text{(E5.12)}$$

$$\text{Pre-prandial insulin need} = -1.9 \times B + 0.0751 \times B^2 + 12.55 \qquad \text{(E5.13)}$$

The basal dose (B) may be assessed by fasting glucose measurements taken at home or in the clinic, the expected pre-prandial doses are distributed amongst meal times on an individual basis, although rules of thumb are employed to distribute pre-prandial insulin by default into two doses taken before breakfast and before the evening meal.

The basal prandial regimen separates the basal requirements from the meal time requirements so that the actual distribution of short acting insulin through the day may vary considerably between individuals.

Where home blood glucose monitoring is available it is always used to adjust insulin doses. Where the only available indication of control is a HbA_{1c} blood test, it must be used to estimate whether doses should be raised over all. The presence of symptoms, in particular recent nocturia with urination and thirst (especially if more than twice in one night), is also an indication that insulin needs to be increased.

In these cases, the system attempts to approach the default doses by gradual increments, or in severe cases, near default doses may be advised immediately, with special instructions to monitor for hypoglycaemia and check the hypoglycaemia with extra food if necessary. The food may subsequently be reduced gradually as easily as insulin may be increased.

Timing of Insulin Doses by Default

The primary aim is to normalise the fasting blood glucose, so the long acting dose is incremented first. Ideally, the long acting dose should be taken before bed, so that the slight peak of insulin release corresponds to a period of rising blood glucose (the dawn effect). Once the dose reaches estimated default levels (E5.10), with instability still present, the long acting dose is split into two; a morning dose and a before bed dose.

The distribution of the short acting insulin should depend on the relative sizes of daily meals. In the absence of any information to the contrary, a slightly higher dose should be given before breakfast as the breakfast meal requires most insulin. Short acting insulin should only be increased with care and based on home blood glucose monitoring.

EVALUATION AND VALIDATION

The amount of evaluation and validation carried out in each of the areas recommended by Berry and Hart (1990 ch. 2) varies. A summary of progress in each area is now followed by suggestions for future evaluation and validation.

The Quality of the System's Advice and Decisions

One evaluation study to compare decisions made by physicians of different levels of experience with the decisions of the decision support system was carried out (see below). Informal analysis of the decisions made by the system when used in the clinic setting is less systematic and does not follow the rules of designing experiments. Therefore, general comments only will be given about the agreement between physicians and the system.

In straightforward cases where data is available on home blood glucose monitoring and long term control has been assessed by HbA1c, the system agreed with the decisions of the physicians approximately 90% of the time. The disagreements usually occurred because of physician interpretation of the patient's information. When told of the decision support system's advice in cases of disagreement the system's suggestions were rated as acceptable in 100% of cases.

In cases with less data on HBGM there was considerably more disagreement on advice. Some physicians preferred to adopt an education strategy, using a high HbA1c to jolt patients into regular HBGM, with advice offered on what to do with the results in some cases. Others took the view that intervention had to be taken immediately and preferred to dictate new therapy even in the absence of HBGM to guide them. The choice of policy rests with the physician's assessment of the patient's interest in diabetes control and compliance. This is extremely difficult to include in a decision support system.

The line taken by the system was to use the default reasoning for insulin therapy outlined above. Oral therapy could be altered on a clinic fasting blood glucose alone and so was not considered such a problem as the clinic FBG is always available except for patients who had mistakenly eaten breakfast (this assumes a morning clinic of course).

In general terms there was roughly 50% agreement with the suggestions given by the system in cases where no home glucose monitoring was recorded. The future policy of the system may be to ask for the view of the physician on whether to suggest alterations or advise a course of HBGM and a further consultation three months later.

Evaluation so far: A knowledge-based validation exercise

In order to assess the level of agreement between physicians and the computer in the early stages of development a simple experiment was designed. A set of test cases was sent to eight 'expert' physicians for their assessment and recommendations for management, seven of the eight replied. The test cases were lifted from recorded consultations with actual patients. The usual precautions to provide patient anonymity were observed.

Four of the physicians were of a senior level (consultant or senior registrar) and three were junior registrars or senior housemen. In addition, five of the physicians came from a clinic which relies heavily on the basal prandial regimen while the other two were involved in a clinic which mainly uses soluble isophane or premixed insulin regimens.

Eight test cases were included in the experiment covering the range of possible therapies available in the expert system at that time. The main therapeutic variations occurred in the insulin treated patients, although qualitatively the advice offered was consistent in all cases. The quantitative amounts by which to change insulin and whether to change to a different regimen differed considerably between physicians.

There was less disagreement between physicians for tablet-treated patients, merely preferences for different types of sulphonylureas, although one important outcome of the tablet-treated cases (and those on diet alone) was the preference in 6 out of the 7 physicians for metformin treatment as the first therapeutic option for obese type II patients. This preference and consensus view was subsequently added to the system.

The correctness of the reasoning techniques used was not assessed directly as the reasoning techniques used were established rule-based inference techniques which have been assessed elsewhere. The correctness of rule-based approaches to medical knowledge-based systems in general has been a subject of interest for some time (Davis et al 1977). Little may be added to this debate by the present work, save to say that rule-based systems provided a suitable platform for the development. Correctness of reasoning is difficult to quantify. It is not merely validation that the outcome is acceptable but that the methods of achieving an acceptable outcome are sound and safe.

The correctness of reasoning is closely related to explanation. The latest clinic system includes an explanation module; these explanations may be rated by clinicians who use the system. No other contrived methods of assessing correctness of reasoning have been used.

With reference to common usability criteria, the system fares reasonably well. It is recognised that formal evaluation and validation techniques are required in order to qualify this statement and such experiments are suggested below and in chapter 6. The interface is largely menu-driven. Exceptions are the occasional numerical and text input for insulin doses, name and identification number of patients etc. The core concepts of data entry and response should be readily recognisable to all trained physicians, whether they have a special interest in diabetes or not. There is a high degree of consistency in the type of information and data entry methods: the use of meal times as a basis is intuitive to the physicians involved in diabetes care. There are only five keys or key combinations required to use the system, although further options are available as users become more experienced: TAB to move between fields, RETURN to select

a menu item, CTRL+RETURN to complete a section and the up and down cursor control keys for menu selection. Help and Explanation are available at all stages by pressing keys F1 and F3 respectively. Once these key combinations are learnt the system may be used with confidence.

A special ESCAPE menu is provided when users press the escape key. The options available are: continue, save the consultation, load a consultation, return to the main section (screen) or exit the system.

Some sections are divided into layers of data entry, it is possible to step through layers in either direction by pressing the PAGE UP (PgUp) or PAGE DOWN (PgDn) keys. Layering of data entry is kept minimal; at most 3 layers are used at any one time so that physicians do not forget where they are. A label at the top of the screen displays the current patient's name and the current knowledge base module.

An area where some improvement could be made is in error correction. Slips may often be corrected by using PgUp and PgDn to move between layers of sections. In other cases mistakes may be wiped by pressing escape and selecting "return to main screen" from the options.

Evaluation techniques used so far have been limited to system-walk-through techniques. Positive reactions were forthcoming from physicians at the sessions, but some did express the worry that it would slow them down considerably.

Proposed further evaluation will be by hands-on use by physicians. Formal observation (possibly video recorded) of how consultations are changed by the introduction of the system would be useful. It would probably not be ethically desirable to use real patients in this type of experiment, so an actor could be used to represent the patient first in a normal consultation and second, in a computer-aided consultation. Time spent discussing each area of diabetic control could be recorded and questionnaires could be answered about the feeling of satisfaction felt in both cases.

Once initial tests had been conducted and possibly modifications made to the system, real patients could be used in the experiments. Their responses to questionnaires would be more useful than those of an actor.

Simple experiments, comparing 2 or more versions of the system or an aspect of the system could be a possibility. For example, one version of the system could give spontaneous explanation whilst the other could only give explanations on request.

An experiment to measure the normalised performance ratio (NPR - chapter 2) could be designed. Different tasks ranging from entering a patient's weight in kg to a completion of an entire consultation could be used to assess a value of beta for the system. Time restrictions make it impossible to include results of such an experiment here.

Performance and System Efficiency

Performance measures commonly carried out on interactive, "real-time" computer systems include response time and time delay for operations such as requesting help.

The delay for initial setting up of files etc. and the delay which occurred between sections (modules) of the program as it currently stands are listed in table 5.14. The minimum delay occurred when no data were entered within the module, the maximum delay corresponds to completion of all the data entry sections. In principle, the mean delay could be calculated over a minimum of 5 or so typical consultations but would lie somewhere near to the maximum value in normal circumstances. Times are rounded to the nearest 1/100 second. The mean delay time for initial set up (of data files etc.) taken over 4 measures was 25.30 ± 0.30 seconds.

Table 5.14 Delays for accessing modules from the main driver module

Module	minimum delay (s)	maximum delay (s)
history	1.99	10.51
status	1.71	10.40
therapy	1.59	10.32
HBGM	1.76	10.49
clinic	2.13	10.87
hypos	1.78	10.57
diet	1.57	10.39
administration	2.07	11.06
mean	1.83	10.58
sd	0.20	0.24

Table 5.15 - time delays in receiving help and explanation

section	help	explanation
general health	0.31	14.78
weight	0.30	14.49
symptoms	0.28	6.20
symptoms(repeat)		5.85
complications	0.29	5.92
complications(repeat)		5.93
smoking	0.32	15.07
aim of therapy	0.31	15.06

The results of table 5.15 were puzzling at first until the system organisation and memory usage were taken into consideration. The help sub-system utilises a library of files and is permanently built into the shell of the system, the times to access the library are therefore much faster and less variable than times to access the explanation sub-system. The explanation sub-system has been added on in the development; normal explanation facilities merely display the rule currently under execution with the option to trace back the logic of why the rule is in execution. The explanation sub-system now consists of a knowledge-base which is called with the parameter of the name of the item currently highlighted for data entry. A file is then assigned from another library, known as the report library, and that is displayed. The reason for the high variability of the delay is due to the memory organisation of the system. The explanation knowledge-base remains resident in memory but for some reason takes various times to

execute. In a further experiment, explanation was requested 10 times in succession from the same section. The results in table 5.16 show that the delay falls to a reasonably constant value of around 4 seconds after 3 requests. A fully developed system would need to employ an explanation subsystem similar to the help library, thus reducing the delay to acceptable levels.

Table 5.16 Course of delays to receipt of explanation from one section.

Request number	Delay (s)
1	12.57
2	12.19
3	3.55
4	3.62
5	3.76
6	4.42
7	4.62
8	3.94
9	4.14
10	4.52
mean ± sd	5.73 ± 3.34
mean ± sd	4.07 ± 0.39 (ignoring first two values)

Whilst no hard and fast rules apply to acceptable delays within computing systems, delays longer than 1 or 2 seconds should be avoided if possible. Delays as long as 25 seconds for a one-off occurrence such as initialisation may be acceptable but delays of 10 seconds or more every time a module is used or explanation is requested would almost certainly be unacceptable for actual use in the clinic by physicians.

The current technology is not capable of great improvement as it has already been optimised. Two methods for improvement of the response times exist: transfer the system to faster hardware or software platform, or rewrite the software with optimisation and better use of memory management, probably in a low level language such as C or Pascal.

Cost Effectiveness

This is possibly the most difficult area of evaluation to perform as an assessment needs to be made of the financial value of the decision support system. What price more effective diabetes care? The cost-effectiveness of the system depends not only on base costs of buying and

maintaining hardware and software - remember performance improves as systems get faster - but also on the time spent by physicians using the system. In order to be cost effective systems should not make consultations longer than they were prior to the introduction of the systems.

Cost-effectiveness is closely linked with performance, as outlined above. A compromise situation often has to be sought with acceptable performance at acceptable cost. Estimation of software costs at various stages of the development may be aided by the use of a model, several models are described and a model is proposed by Mohanty (1981). Mohanty suggests that the cost of software is perhaps most closely aligned with its quality, although that point is highly debatable. Newly developed formal techniques can and will become standard software development techniques in so-called safety-critical fields such as medicine. They need not be costly in real terms. Their use in conjunction with proven software engineering techniques, such as following a development life cycle of requirements, design, development and evaluation, will ensure that the right product is delivered in the quickest time with the least errors. Cost can be estimated in man-units of effort but the productivity of individuals will affect this assessment and it is therefore difficult to be accurate. Another major problem, especially in medicine is the measurement of the utility of software and computer use in general. Some people still say that computers can do nothing that cannot be done with paper which is, in my opinion, absolute nonsense.

KNOWLEDGE BASE MAINTENANCE

A knowledge base can never be complete. As new knowledge is created by experiment or experience, so knowledge has to be added to a knowledge based system. A piece of knowledge can never be considered as static. All knowledge is to some extent changable with time. therefore, knowledge bases need to be structured so that their knowledge can be updated easily and safely, without affecting the knowledge already in the system.

The method used to maintain the current knowledge-base has been manual addition of rules. Although a selection of test cases exist and are regularly run through the system to check that new rules have not affected other sections, the perils of such additions of rules are well known (Compton and Jansen 1990).

Recommended essential development of a delivery system would include either ripple-down rule organisation or explanation-based learning (see ch. 2). The major problem with explanation-based learning is that the expert has to enter rules manually. The development of voice recognition may be the only spur for physicians to allow the type of interaction necessary for decision support to reach the clinic. New generation graphical user interfaces (GUIs) are rapidly approaching which may feature artificial speech generation and rudimentary voice recognition in the fashion of an animation (McMillan and Harris 1990) although the technology may be some time reaching the market place.

CHAPTER 6 - CONCLUSIONS

CLINICAL IMPACT

The possible clinical impact of the two systems is difficult to estimate at this very early stage. Still fewer than fifty patients have had experience of using POIRO, but the favourable comments from the vast majority of these people undoubtedly shows that a decision support system for everyday use would be popular. Indeed, many of the patients who used the system for a time have expressed a desire to carry out extended trials of the system; this may be the next step in the evaluation. The actual clinical impact, during the trial phase was an increased health care professional workload; this was due to increased demand for reassurance from wary patients when insulin doses were changed. Extra work was also required to cope with the collection and assimilation of data. In the long term, however, patients would be expected to follow the advice between clinic attendances with confidence and should not encounter problems which previously might have resulted in a physician call; for instance a short term illness or change in diet or lifestyle (going on holiday for example) is quite easily addressed by POIRO provided glucose measurements are carried out. The benefits to the physician in these type of time savings is probably minimal, but the extra availability of information, collected and transferred by the system, should provide enormous benefits to epidemiological studies. There is also potential for the use of POIRO within clinical trials of different insulin preparations, lengths of needles for injections and so on. POIRO now offers a facility to carry out controlled experiments in dose adjustment and at the very least provides for the essential collection of data.

The completed clinic system (PRESTO) would permit intelligent use of the extra data generated by POIRO during the time of the consultation. A set of graphical routines, statistical routines and the further employment of the standalone DSS with data entry from the POIRO system should enhance the decision data of the physician. The PRESTO system as it stands will not gain clinical approval for the simple reason that its performance is too slow. Three methods of

improving the performance are possible: The first is to implement the system directly in a low level programming language such as clipper or C. This has obvious advantages of speed but, unless the inference engine is re-implemented in the code, it loses the possibility of quick modifications of the rule-base. The second alternative is dependent on new versions of the expert system shell Xi+. The system has been transferred successfully to the new version (3.5) of Xi+ which runs under Windows 3. The efficient use of extended memory for storing knowledge bases may improve the time lags between loading knowledge bases to a usable stage. The third, and probably most attractive, solution would be to move the knowledge into a module of another decision support system, (the only realistic current candidate being the Oxford System of Medicine). This would have advantages that the problems of storage and speed would have been addressed, and also the integration with general medicine would be effected. This is a serious, although often neglected, problem with most domain specific applications intended for use in general practice. The Advanced Informatics in Medicine (AIM) second phase includes a new project - Dilemma - which builds on the research which went into the OSM in order to provide facilities for decision support in general practice medicine. A diabetes module for the new system is planned and the integration of the PRESTO system would have obvious mutual benefits of interacting technology and clinical research.

Lessons Learnt

The main lesson to be gained from the development work is the importance of listening to the end user (i.e. patients) in order to understand their likes and dislikes. Early trials of the hand held device paid off handsomely in the development of that system. Likewise, early display of the physician based system to practising diabetologists and other interested parties from both the computer science and clinical fields produced advice on information omitted and also some encouraging comments that the system was heading in the right direction.

The structure of knowledge in relation to the timing of meals and therapy has been the crucial aspect of the system. Simple rules have been generalised to fit into the times of day at which

the patients take their meals. Utilising longitudinal data will be a major challenge to further developments of the system along with integration into existing data base information.

The Way Forward

Simplicity of use must be the major consideration in computerised tools for use in many areas but especially one as critical and widespread as medicine. Patients should be educated by any tools. Advice should be offered in support of their own knowledge enabling them to be self reliant in future.

The clinic system will benefit greatly from an improved user interface and improved interaction within the program allowing simple "what if" type questions to be asked. A graphical interface has potential for tasks such as entering portions of food in the dietary assessment knowledge base and especially for graphical interpretation of longitudinal information on clinic measurements such as haemoglobin A_{1c} and body weight.

One particular aspect of the system which could be greatly enhanced by graphics is the explanation of dose changes. If a picture of a patient's current situation could be shown to change graphically to lower (or higher) glucose values as insulin was increased (reduced) it may give the patient more insight into exactly which blood glucoses are affected by which insulin doses. This would be especially useful in more complicated insulin regimens.

Compatibility

A major problem throughout the development of the two systems was the incompatibility of the operating systems of the two computers. The CP/M operating system of the Epson device and the MS-DOS PC both support Turbo Pascal so that was a distinct advantage but the file structures were different and several other odd differences in code came to notice. The POIRO system has since been re-implemented on an IBM-compatible palm-top computer running MS-DOS. However, the lack of a touch-sensitive screen on the palm-top makes it a far more difficult system to use.

This merely highlights the importance of providing compatibility between health care systems for general use. Similarly, while different health authorities, and even different departments within hospitals, are using different coding systems and computer hardware and software, the problems of information transfer are not going to be resolved.

Individual patient records stored on smart cards are currently a popular option, especially in France and Germany where large scale trials have been carried out. This still requires compatibility of the health care professionals' systems to be able to retrieve data relevant to their speciality. The password protection of certain sections of the cards provides a method of integrating all personal information on one card, including financial and health data. There is still the major problem of loss of the cards, so some central "back-up" store of information would need to be kept and updated by all the remote sites, or otherwise kept centrally and distributed over networks. Eventually we may see this taken a step further with implanted electronic memory chips within the human body, with specialities related to individual health problems.

Diabetes Therapy in the 90s

As we move further into the last decade of the century, we are more and more able to understand the human body and the treatment of chronic diseases. Much recent optimism has been aroused by pancreas and islet cell transplants. Research into a hybrid artificial pancreas continues to arouse hopes that implanted "bionic" devices may provide the best solution to insulin replacement therapy. The technology has some way to go before the treatment is commonplace. Transplants will only be a serious option for patients with renal failure as the transplants are carried out in conjunction with kidney transplants.

People with diabetes are now able to live longer and enjoy more freedom during their lives than they were even twenty years ago. During the next few years the results of large, prospective, randomised trials are expected. If, as expected, these results show the desirability of intensive

insulin replacement therapy against conventional therapy the computer system outlined in this thesis should be at the forefront of the provision of such care.

The present work could, in any case, provide vital information about glucose regulation in diabetes for any proposed therapeutic options. The knowledge of this is, at this stage, still a largely misunderstood area.

The inherent instability of type I diabetes has aroused suspicions of chaos (Gleick 1990). Modelling of diabetes should concentrate on non-linear dynamics; it may soon be possible to define a family of chaotic attractors which typify the course of type I diabetes but this is merely conjecture. I am very cautious of expounding this theory too much as chaos is unfortunately a much abused and misunderstood theory in many other sciences. This line of research should reasonably be put to an experienced chaos expert and could prove to be an interesting area for further study.

It has been shown for decades now that traditional diabetes care is capable, in the right hands, of good control. The employment of these two systems should provide that quality of control in many more cases than at present. I hope that the results of this research work can help to provide the basis for a flexible, robust, well-validated intelligent support systems, firstly for diabetes but later for many other chronic diseases which require self-management and therapy adjustment.

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APPENDIX 1 - TECHNICAL SPECIFICATION OF THE EHT-10 USED AS THE POIRO PROTOTYPE

Main CPU : μPD70008 C-MOS (Z-80 compatible). CLK= 3.6864 MHz.

Slave CPU : CPU7508 4-bit C-MOS. (Controls key input, clock, power supply and serial communications)

ROM : System ROM μPD23C1000G CMOS 128 KB. Application ROM of 128 KB is supported (CMOS structure with access time faster than 200 ns).

Main Memory : Can be extended up to 256 Kbytes, up to 232 KB can be used as a RAM disk.

Display : 154 x 84 dot LCD and LCD controller T6963. Driver X:T7778 x 4, Y:T691 x 1. Size of screen is 12 columns x 14 lines or 24 columns x 10 lines in horizontal mode.

Input : Touch Panel with 14 x 5 input points. Area of Touch keys 10.5 x 9.35 mm.

Interfaces : RS-232C I/F, cartridge I/F, bar code I/F and IC card I/F for external interface connection. The cartridge I/F consists of 4 modes (HS mode, DB mode, IO mode, OT mode).

Power supply : Nickel-cadmium battery pack as a main battery charged through an AC adaptor. Nickel-cadmium sub-battery performs RAM backup as a design safeguard, even when the main battery is discharged, RAM backup is supported.

Operating System : Extended CP/M Version 2.2.

APPENDIX 2 - THE FIXED DATA FILE

Several items of information need to be initialised by the physician and then transferred back and forth between the physician's PC and the EHT-10. These items are further described in the main text. At a clinic visit the currently derived advised doses are written to the fixed data file and uploaded along with all the originally prescribed information.

Surname
First Name
00004 (id number)
0 (Sex: 0=female, 1=male)
180 (height cm)
84 (weight kg)
2000 (diet kcal)
200 (dietary CHO g)
75 (activity level %)
Dr. Holman (supervising doctor)
0865 224597 (contact number)
Jill = 64937 (second contact number)
01/11/90 (date of next clinic)
14:30 (time of next clinic)
5.5 (target FBG)
20.0 (maximum allowed blood glucose)
2.5 (minimum allowed blood glucose)
Actrapid (short acting insulin regimen)
(008,014,002) (Dose, Maximum, Minimum) (pre-breakfast)
(012,018,006) (" " ") (pre-lunch)
(018,027,009) (" " ") (pre-evening meal)
(000,000,000) (" " ") (pre-bed)
(blank space for intermediate acting insulin regimen)
Ultratard (long acting insulin regimen)
(006,012,000) (" " ") (pre-breakfast)
(000,000,000) (" " ") (pre-lunch)
(000,000,000) (" " ") (pre-evening meal)
(006,012,000) (" " ") (pre-bed)
[Control variables]
meal 0.00, 0.60, 1.00, 1.40
exercise 1.20, 1.10, 1.00, 0.75
health 1.00, 1.20, 1.50
supplement 2.00, 0.75, 3.50, 0.90, 10.00, 1.10, 15.00, 1.15
gluranges 1.00, 2.00, 1.00, 2.00, 0.05, 0.10
sensitivity 1.00, 0.00, 4.00
difftimes 60, 30, 420, 10, 180, 240
stats 2.00, 3.50
0 (advice status 0=off, 1=on)

APPENDIX 3 - COMMUNICATIONS ROUTINES.

Constants used:

The following is a refresher of the commonly used names for constants in the extended ASCII character set reserved for communications.

NULL = $00 **SOH = $01** **STX = $02** **ETX = $03** **EOT = $04**

ENQ = $05 **ACK = $06** **CR = $0d** **ESC = $1b**

As well as these there are some slightly non-standard constants

ECODE0 = $11 **ECODE1 = $12** **ECODE2 = $13**

And a few other constant values which are used in the protocol

block_size = $80 (128 decimal) - the size of the block used in untyped files by default in CP/M (the block size for blockread / blockwrite may not be defined by the user in CP/M as it may in MS-DOS).

password = 'password' - this string is sent to establish the authorisation of the user of the PC to access data stored on the EHT-10.